

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 45/06, 31/585, 31/41	A2	(11) International Publication Number: WO 96/40255 (43) International Publication Date: 19 December 1996 (19.12.96)
(21) International Application Number: PCT/US96/08709 (22) International Filing Date: 5 June 1996 (05.06.96) (30) Priority Data: 08/486,085 7 June 1995 (07.06.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/486,085 (CON) Filed on 7 June 1995 (07.06.95) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): EGAN, James, J. [US/US]; 555 Cherry Street, Winnetka, IL 60093 (US). MCMAHON, Ellen, G. [US/US]; 7925 Camelot, St. Louis, MO 63123 (US). OLINS, Gillian, M. [US/US]; 17507 Summit View, Glencoe, MO 63038 (US). SCHUH, Joseph, R. [US/US]; 2055 Rurline Drive, St. Louis, MO 63146 (US).	(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680- 5110 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST (57) Abstract <p>A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9α,11α-substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION
THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-
STEROIDAL ALDOSTERONE ANTAGONIST

5

Field of the Invention

Therapeutic methods are described for treatment of
cardiofibrosis and cardiac hypertrophy. Of particular
10 interest are therapies using an epoxy-containing steroidal
aldosterone receptor antagonist compound such as
epoxymexrenone in combination with an angiotensin II
receptor antagonist compound.

15

Background of the Invention

Myocardial (or cardiac) failure, whether a
consequence of a previous myocardial infarction, heart
disease associated with hypertension, or primary
20 cardiomyopathy, is a major health problem of worldwide
proportions. The incidence of symptomatic heart failure has
risen steadily over the past several decades.

In clinical terms, decompensated cardiac failure
25 consists of a constellation of signs and symptoms that
arises from congested organs and hypoperfused tissues to
form the congestive heart failure (CHF) syndrome.
Congestion is caused largely by increased venous pressure
and by inadequate sodium (Na⁺) excretion, relative to dietary
30 Na⁺ intake, and is importantly related to circulating levels
of aldosterone (ALDO). An abnormal retention of Na⁺ occurs
via tubular epithelial cells throughout the nephron,
including the later portion of the distal tubule and
cortical collecting ducts, where ALDO receptor sites are
35 present.

ALDO is the body's most potent mineralocorticoid
hormone. As connoted by the term mineralocorticoid, this

steroid hormone has mineral-regulating activity. It promotes Na^+ reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive tissues. ALDO regulates Na^+ and water resorption at the expense of potassium (K^+) and magnesium (Mg^{2+}) excretion.

ALDO can also provoke responses in nonepithelial cells. Elicited by a chronic elevation in plasma ALDO level that is inappropriate relative to dietary Na^+ intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

15

Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as non-renin-dependent factors (such as K^+ , ACTH) that promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine its plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

25

The renin-angiotensin-aldosterone system (RAAS) is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension. Activation of the renin-angiotensin-aldosterone system begins with renin secretion from the juxtaglomerular cells in the kidney and culminates in the formation of angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic

30

35

effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II binding at its receptors is a viable approach to inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such peptidic compounds are of limited use due to their lack of oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, early descriptions of such non-peptidic compounds include the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid which has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and *in vivo* tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247(1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and *in vivo* tests [A. T. Chiu et al, European J. Pharmacol., 157, 31-21 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant

decrease in mean arterial blood pressure in conscious hypertensive rats. Other families of non-peptidic angiotensin II antagonists have been characterized by molecules having a biphenylmethyl moiety attached to a heterocyclic moiety. For example, EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole. U.S. Patent No. 4,880,804 to Carini et al describes a family of biphenylmethylbenzimidazole compounds as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

Many aldosterone receptor blocking drugs are known. For example, spironolactone is a drug which acts at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosterone-related diseases such as liver cirrhosis and congestive heart failure [F.J. Saunders et al, Aldactone: Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day] were administered to a spironolactone-intolerant patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. J. Med., 314 (4), 343-345 (Jul-Aug, 1986)]. It has been recognized that development of

myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to excessive collagen deposition [D. Klug et al, Am. J. Cardiol., 71 (3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G. Brilla et al, J. Mol. Cell. Cardiol., 25(5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)].

Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

Moreover, although ACE inhibitors effectively block the formation of angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, J. Endocrinol., 91, 457-465 (1981)]. A similar effect has been observed for patients with myocardial infarction receiving zofenopril [C. Borghi et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. This phenomenon has been termed "aldosterone escape".

Another series of steroidal-type aldosterone receptor antagonists is exemplified by epoxy-containing spironolactone derivatives. For example, U.S. Patent No. 4,559,332 issued to Grob et al describes 9 α ,11 α -epoxy-

5 containing spironolactone derivatives as aldosterone antagonists useful as diuretics. These 9 α ,11 α -epoxy steroids have been evaluated for endocrine effects in comparison to spironolactone [M. de Gasparo et al, J. Pharm. Exp. Ther., 240(2), 650-656 (1987)].

10

Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and that

15 aldosterone levels increase as CHF progresses from activation of the Renin-Angiotensin-Aldosterone System (RAAS). Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and

20 transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and

25 spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. Cardiol., 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of captopril and spironolactone was administered and found effective to control refractory CHF without

30 serious incidents of hyperkalemia [U. Dahlstrom et al, Am. J. Cardiol., 71, 29A-33A (21 Jan 1993)]. Spironolactone coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure [A.A. van Vliet et al, Am. J. Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements

35 have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to

determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)].

- 5 Combinations of an angiotensin II receptor
antagonist and aldosterone receptor antagonist, are known.
For example, PCT Application No. US91/09362 published 25
June 1992 describes treatment of hypertension using a
combination of an imidazole-containing angiotensin II
10 antagonist compound and a diuretic such as spironolactone.

Summary of the Invention

A therapeutic method for treating or preventing the progression of cardiofibrosis or cardiac hypertrophy is provided by a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist.

The phrase "angiotensin II receptor antagonist" is intended to embrace one or more compounds or agents having the ability to interact with a receptor site located on various human body tissues, which site is a receptor having a relatively high affinity for angiotensin II and which receptor site is associated with mediating one or more biological functions or events such as vasoconstriction or vasorelaxation, kidney-mediated sodium and fluid retention, sympathetic nervous system activity, and in modulating secretion of various substances such as aldosterone, vasopressin and renin, to lower blood pressure in a subject susceptible to or afflicted with elevated blood pressure. Interactions of such angiotensin II receptor antagonist with this receptor site may be characterized as being either "competitive" (i.e., "surmountable") or as being "insurmountable". These terms, "competitive" and "insurmountable", characterize the relative rates, faster for the former term and slower for the latter term, at which the antagonist compound dissociates from binding with the receptor site.

The phrase "epoxy-steroidal aldosterone receptor antagonist" is intended to embrace one or more agents or compounds characterized by a steroid-type nucleus and having an epoxy moiety attached to the nucleus and which agent or compound binds to the aldosterone receptor, as a competitive inhibitor of the action of aldosterone itself at the receptor site, so as to modulate the receptor-mediated activity of aldosterone.

The phrase "combination therapy", in defining use of an angiotensin II antagonist and an epoxy-steroidal aldosterone receptor antagonist, is intended to embrace administration of each antagonist in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended to embrace co-administration of the antagonist agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each antagonist agent.

The phrase "therapeutically-effective" is intended to qualify the amount of each antagonist agent for use in the combination therapy which will improve cardiac sufficiency by reducing or preventing the progression of myocardial fibrosis or cardiac hypertrophy.

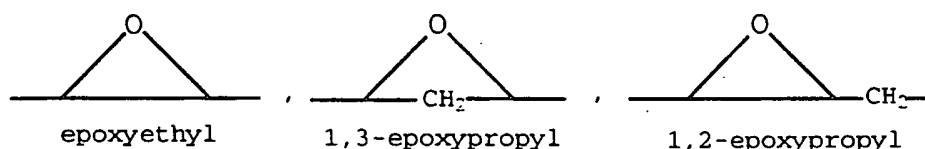
Another combination therapy of interest would consist essentially of three active agents, namely, an AII antagonist, an aldosterone receptor antagonist agent and a diuretic.

For a combination of AII antagonist agent and an ALDO antagonist agent, the agents would be used in combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of the AII antagonist agent to the aldosterone receptor antagonist agent. A preferred range of these two agents (AII antagonist-to-ALDO antagonist) would be from about one-to-one to about fifteen-to-one, while a more preferred range would be from about one-to-one to about five-to-one, depending ultimately on the selection of the AII antagonist and ALDO antagonist. The diuretic agent may be present in a ratio range of 0.1-to-one to about ten to one (AII antagonist to diuretic).

Detailed Description of the Invention

Epoxy-steroidal aldosterone receptor antagonist compounds suitable for use in the combination therapy consist of these compounds having a steroidal nucleus substituted with an epoxy-type moiety. The term "epoxy-type" moiety is intended to embrace any moiety characterized in having an oxygen atom as a bridge between two carbon atoms, examples of which include the following moieties:

10



The term "steroidal", as used in the phrase "epoxy-steroidal", denotes a nucleus provided by a cyclopentenophenanthrene moiety, having the conventional "A", "B", "C" and "D" rings. The epoxy-type moiety may be attached to the cyclopentenophenanthrene nucleus at any attachable or substitutable positions, that is, fused to one of the rings of the steroidal nucleus or the moiety may be substituted on a ring member of the ring system. The phrase "epoxy-steroidal" is intended to embrace a steroidal nucleus having one or a plurality of epoxy-type moieties attached thereto.

Epoxy-steroidal aldosterone receptor antagonists suitable for use in combination therapy include a family of compounds having an epoxy moiety fused to the "C" ring of the steroidal nucleus. Especially preferred are 20-spiroxane compounds characterized by the presence of a 9 α ,11 α -substituted epoxy moiety. Table I, below, describes a series of 9 α ,11 α -epoxy-steroidal compounds which may be used in the combination therapy. These epoxy steroids may be prepared by procedures described in U.S. Patent No. 4,559,332 to Grob et al issued 17 December 1985.

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
1		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ -lactone, methyl ester, (7 α ,11 α ,,17 α)-
2		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 α ,11 α ,17 α)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
3		3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -lactone, (6 β , 7 β , 11 β , 17 β) -
4		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-(1-methylethyl) ester, monopotassium salt, (7a, 11a, 17a) -

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
5		Pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7a,11a,17a)-
6		3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g-lactone (6a,7a,11.a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
7		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6a,7a,11a,17a)-
8		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6a,7a,11a,17a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
9		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g lactone, (6a,7a,11a.,17a)-
10		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, ethyl ester, (7a,11a,17a)-

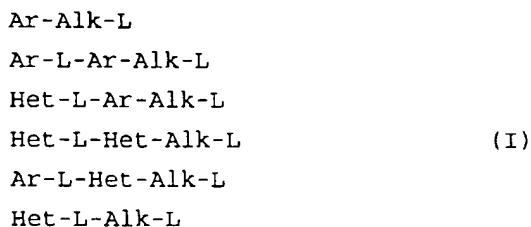
TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
11		pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, 1-methylethyl ester, (7a,11a,17a) -

Angiotensin II receptor antagonist compounds suitable for use in the combination therapy are described in Table II, below. Preferred compounds for use in the combination therapy may be generally characterized structurally as having two portions. A first portion constitutes a mono-aryl-alkyl moiety, or a bi-aryl-alkyl moiety, or a mono-heteroaryl-alkyl moiety, or a bi-heteroaryl-alkyl moiety. A second portion constitutes a heterocyclic moiety or an open chain hetero-atom-containing moiety.

Typically, the first-portion mono/bi-aryl/heteroaryl-alkyl moiety is attached to the second portion heterocyclic/open-chain moiety through the alkyl group of the mono/bi-aryl/heteroaryl-alkyl moiety to any substitutable position on the heterocyclic/open-chain moiety second portion. Suitable first-portion mono/bi-aryl/heteroaryl-alkyl moieties are defined by any of the various moieties listed under Formula I:

20



25

wherein the abbreviated notation used in the moieties of Formula I is defined as follows:

30

"Ar" means a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being typically fully unsaturated but which also may be partially or fully saturated. "Phenyl" radical most typically exemplifies "Ar".

35

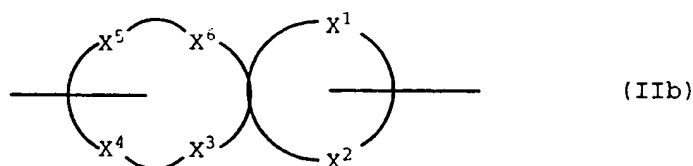
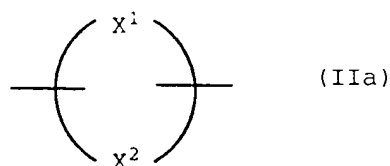
"Het" means a monocyclic or bicyclic fused ring

system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as
5 ring members.

"Alk" means an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms. Typically, "Alk" means "methylene", i.e., -CH₂-.
10

"L" designates a single bond or a bivalent linker moiety selected from carbon, oxygen and sulfur. When "L" is carbon, such carbon has two hydrido atoms attached thereto.

15 Suitable second-portion heterocyclic moieties of the angiotensin II antagonist compounds, for use in the combination therapy, are defined by any of the various moieties listed under Formula IIa or IIb:



wherein each of X^1 through X^6 is selected from $-CH=$, $-CH_2-$,
 5 $-N=$, $-NH-$, O , and S , with the proviso that at least one of
 X^1 through X^6 in each of Formula IIa and Formula IIb must be
 a hetero atom. The heterocyclic moiety of Formula IIa or
 IIb may be attached through a bond from any ring member of
 the Formula IIa or IIb heterocyclic moiety having a
 10 substitutable or a bond-forming position.

Examples of monocyclic heterocyclic moieties of
 Formula IIa include thienyl, furyl, pyranyl, pyrrolyl,
 imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl,
 15 pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl,
 furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl,
 isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-
 triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl,
 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl,
 20 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-
 dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-
 dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl,
 1,4-pyranyl, 1,2-pyranyl, 1,4-pyranyl, pyridinyl,
 25 piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-
 oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl, 1,2,6-oxazinyl,
 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-
 oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl,

1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

Examples of bicyclic heterocyclic moieties of Formula IIb include benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiol-5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

The angiotensin II receptor antagonist compounds, as provided by the first-and-second-portion moieties of Formula I and II, are further characterized by an acidic moiety attached to either of said first-and-second-portion moieties. Preferably this acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

-U_nA (III)

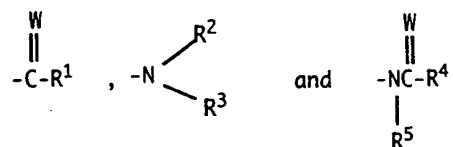
wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the -U_nA

moiety, is intended to embrace chemical groups which, when attached to any substitutable position of the Formula I-IIa/b moiety, confers acidic character to the compound of Formula I-IIa/b. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I-IIa/b to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I-IIa/b has a pK_a in a range from about one to about twelve. More typically, the Formula I-IIa/b compound would have a pK_a in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group (-COOH). Where n is zero and A is -COOH, in the $-U_nA$ moiety, such carboxyl group would be attached directly to one of the Formula I-IIa/b positions. The Formula I-IIa/b compound may have one $-U_nA$ moiety attached at one of the Formula I-IIa/b positions, or may have a plurality of such $-U_nA$ moieties attached at more than one of the Formula I-IIa/b positions. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I-IIa/b may have one or more acidic protons and, therefore, may have one or more pK_a values. It is preferred, however, that at least one of these pK_a values of the Formula I-IIa/b compound as conferred by the $-U_nA$ moiety be in a range from about two to about seven. The $-U_nA$ moiety may be attached to one of the Formula I-IIa/b positions through any portion of the $-U_nA$ moiety which results in a Formula I-IIa/b compound being relatively stable and also having a labile or acidic proton to meet the foregoing pK_a criteria. For example, where the $-U_nA$ acid moiety is tetrazole, the tetrazole is typically attached at

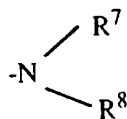
the tetrazole ring carbon atom.

For any of the moieties embraced by Formula I and Formula II, such moieties may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



20

wherein W is oxygen atom or sulfur atom; wherein each of R¹ through R⁵ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR⁶ and



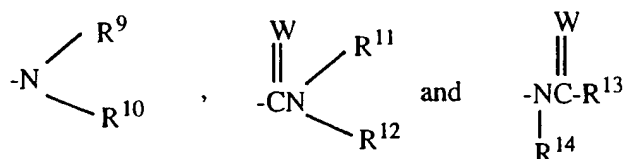
25

wherein Y is selected from oxygen atom and sulfur atom and R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl,

30

arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is further independently selected from amino and amido radicals of the formula

5



wherein W is oxygen atom or sulfur atom;
 wherein each of R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ is
 10 independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl; and wherein each of R² and R³ taken together and each of R⁴ and R⁵ taken together may form a heterocyclic group having five
 15 to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially
 20 unsaturated; wherein each of R² and R³ taken together and each of R⁷ and R⁸ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more
 25 hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The combination therapy of the invention would be
 30 useful in treating myocardial fibrosis or cardiac hypertrophy, particularly left ventricular hypertrophy. The combination therapy would also be useful with adjunctive therapies. For example, the combination therapy may be used in combination with other drugs, such as a diuretic, to aid

in treatment of hypertension.

Table II, below, contains description of
angiotensin II antagonist compounds which may be used in the
5 combination therapy. Associated with each compound listed
in Table II is a published patent document describing the
chemical preparation of the angiotensin II antagonist
compound as well as the biological properties of such
compound. The content of each of these patent documents is
10 incorporated herein by reference.

TABLE II: Angiotensin II Antagonists

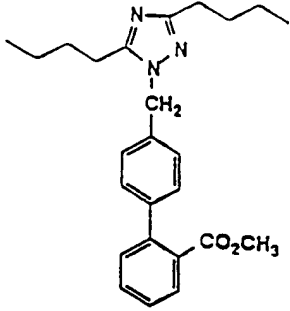
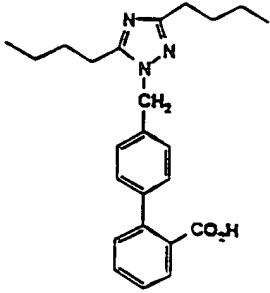
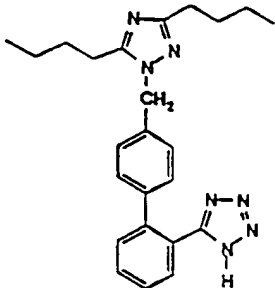
Compound #	Structure	Source
1		WO #91/17148 pub. 14 Nov 91
2		WO #91/17148 pub. 14 Nov 91
3		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

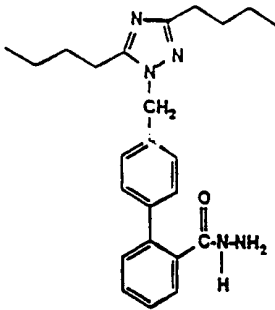
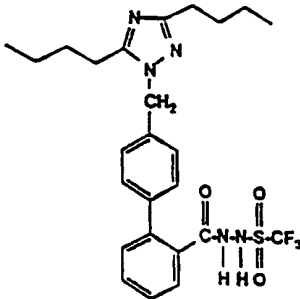
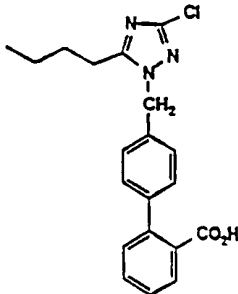
Compound #	Structure	Source
4		WO #91/17148 pub. 14 Nov 91
5		WO #91/17148 pub. 14 Nov 91
6		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

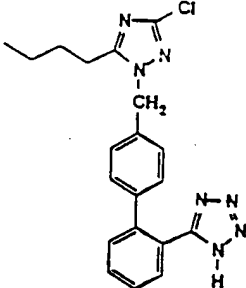
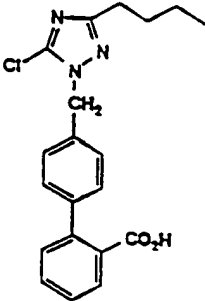
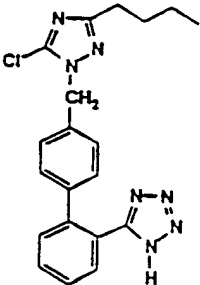
Compound #	Structure	Source
7		WO #91/17148 pub. 14 Nov 91
8		WO #91/17148 pub. 14 Nov 91
9		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

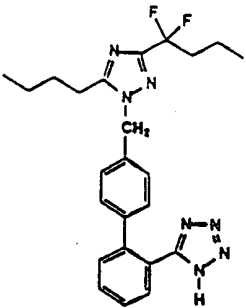
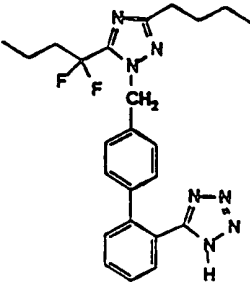
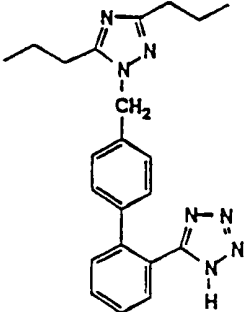
Compound #	Structure	Source
10		WO #91/17148 pub. 14 Nov 91
11		WO #91/17148 pub. 14 Nov 91
12		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

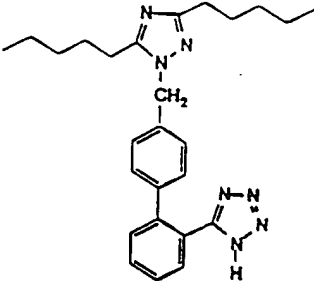
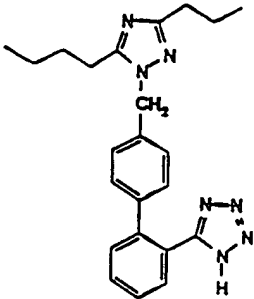
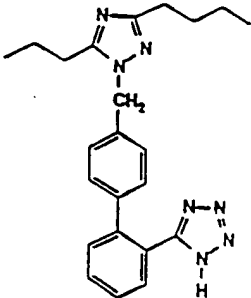
Compound #	Structure	Source
13		WO #91/17148 pub. 14 Nov 91
14		WO #91/17148 pub. 14 Nov 91
15		WO #91/17148 pub. 14 Nov 91

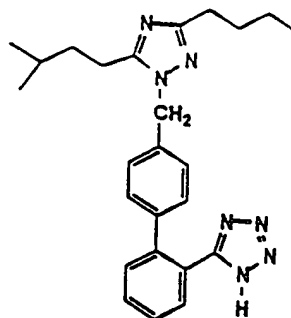
TABLE II: Angiotensin II Antagonists

Compound #

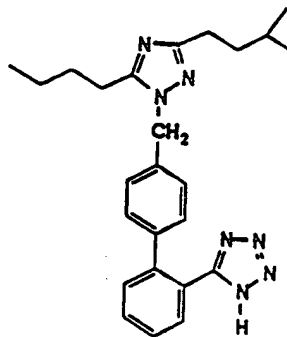
Structure

Source

15

WO #91/17148
pub. 14 Nov 91

17

WO #91/17148
pub. 14 Nov 91

18

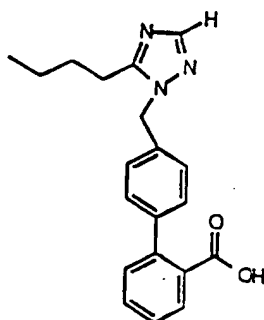
WO #91/17148
pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

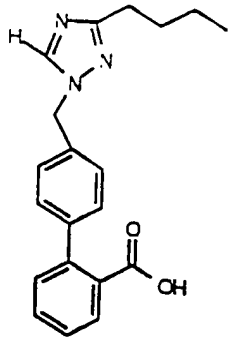
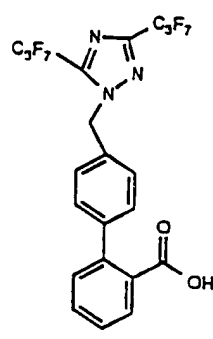
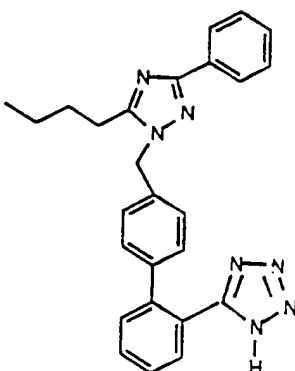
Compound #	Structure	Source
19		WO #91/17148 pub. 14 Nov 91
20		WO #91/17148 pub. 14 Nov 91
21		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

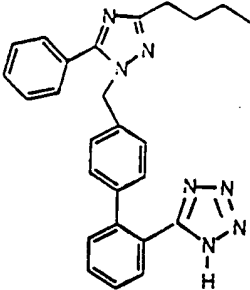
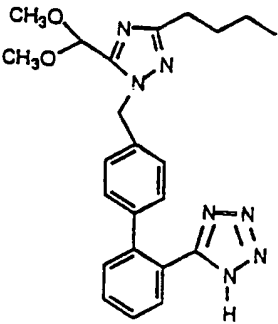
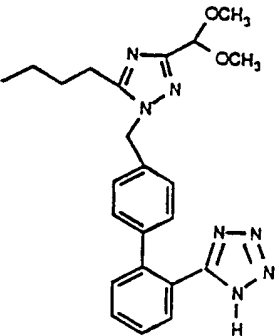
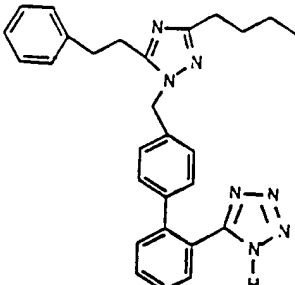
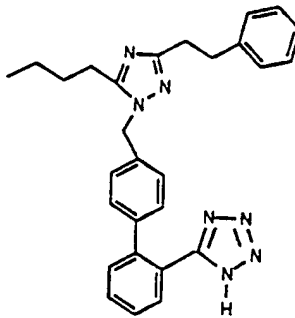
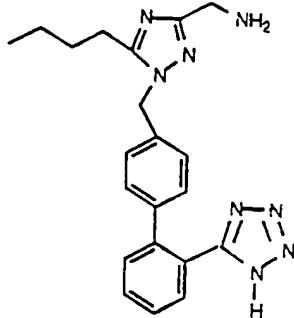
Compound #	Structure	Source
22		WO #91/17148 pub. 14 Nov 91
23		WO #91/17148 pub. 14 Nov 91
24		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
25		WO #91/17148 pub. 14 Nov 91
26		WO #91/17148 pub. 14 Nov 91
27		WO #91/17148 pub. 14 Nov 91

34

TABLE II: Angiotensin II Antagonists

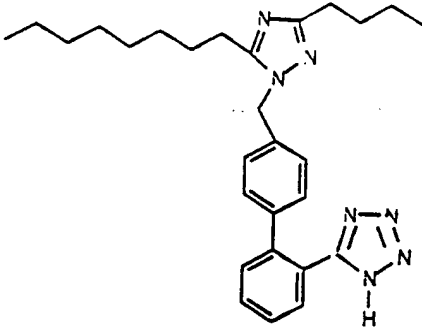
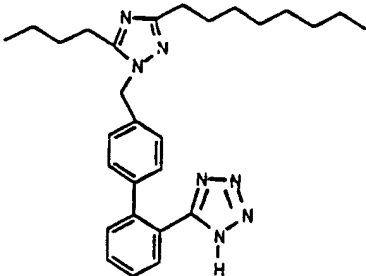
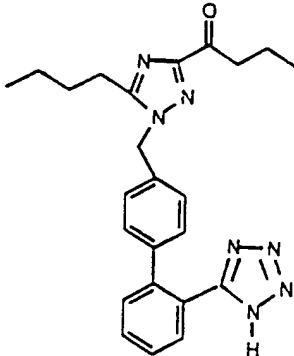
Compound #	Structure	Source
28		WO #91/17148 pub. 14 Nov 91
29		WO #91/17148 pub. 14 Nov 91
30		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

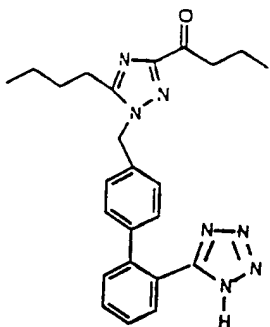
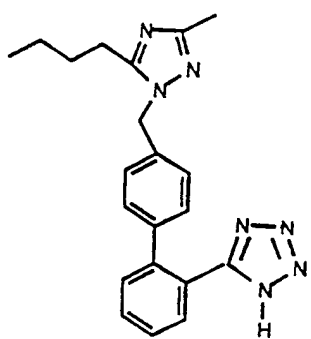
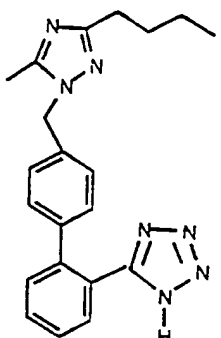
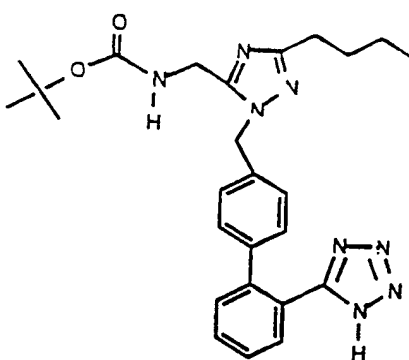
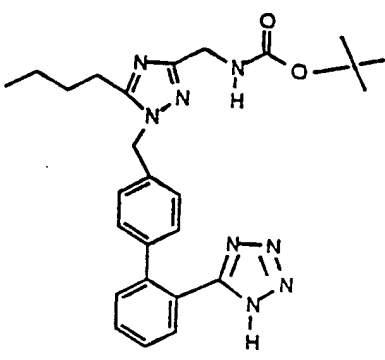
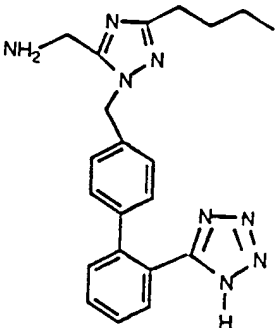
Compound #	Structure	Source
31		WO #91/17148 pub. 14 Nov 91
32		WO #91/17148 pub. 14 Nov 91
33		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
34		WO #91/17148 pub. 14 Nov 91
35		WO #91/17148 pub. 14 Nov 91
36		WO #91/17148 pub. 14 Nov 91

37

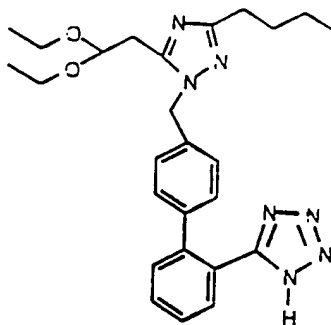
TABLE II: Angiotensin II Antagonists

Compound #

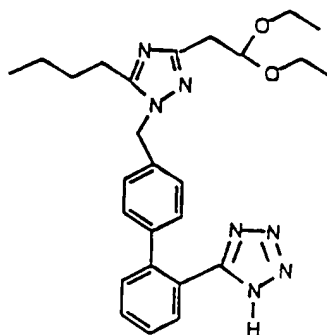
Structure

Source

37

WO #91/17148
pub. 14 Nov 91

38

WO #91/17148
pub. 14 Nov 91

39

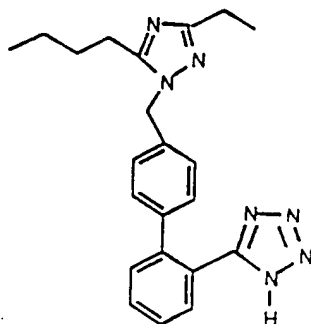
WO #91/17148
pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

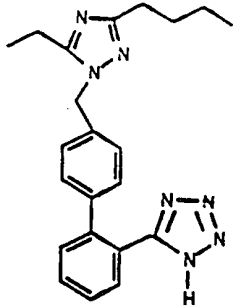
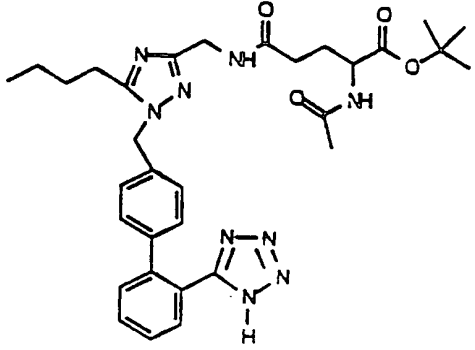
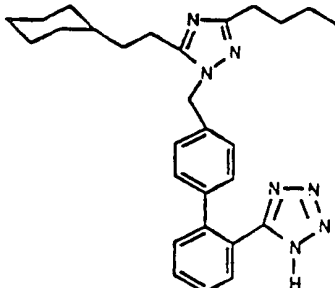
Compound #	Structure	Source
40		WO #91/17148 pub. 14 Nov 91
41		WO #91/17148 pub. 14 Nov 91
42		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

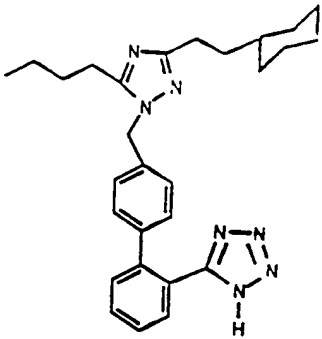
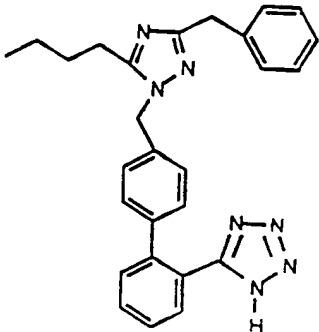
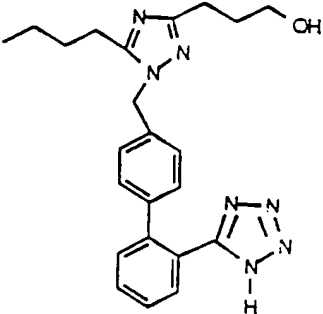
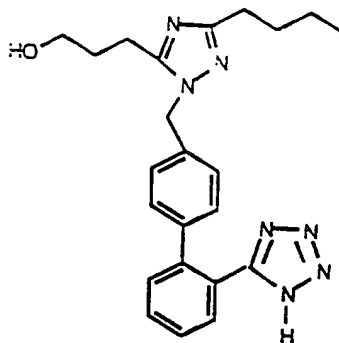
Compound #	Structure	Source
43		WO #91/17148 pub. 14 Nov 91
44		WO #91/17148 pub. 14 Nov 91
45		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

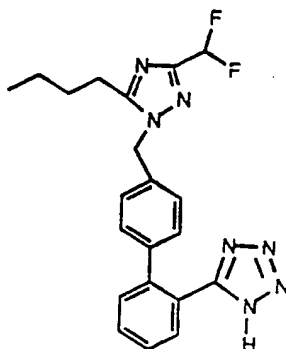
Compound #	Structure	Source
------------	-----------	--------

46



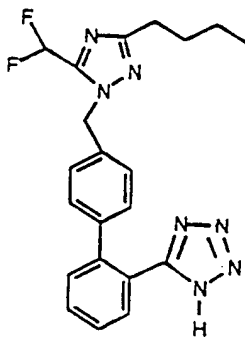
WO #91/17148
pub. 14 Nov 91

47



WO #91/17148
pub. 14 Nov 91

48



WO #91/17148
pub. 14 Nov 91

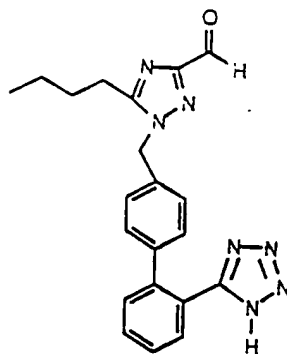
TABLE II: Angiotensin II Antagonists

Compound #

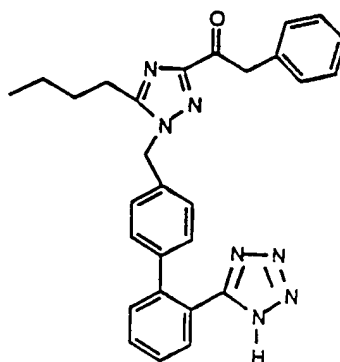
Structure

Source

49

WO #91/17148
pub. 14 Nov 91

50

WO #91/17148
pub. 14 Nov 91

51

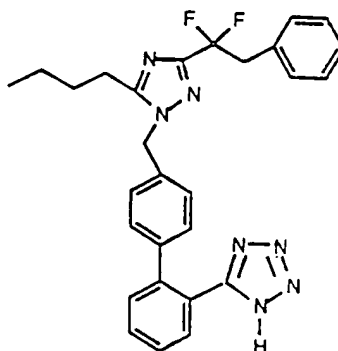
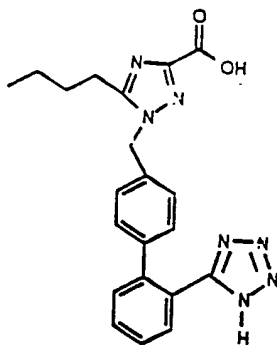
WO #91/17148
pub. 14 Nov 91

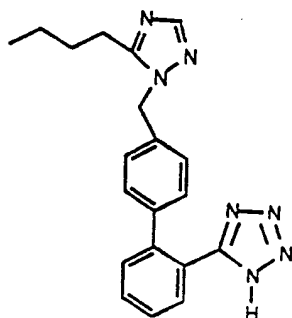
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

52

WO #91/17148
pub. 14 Nov 91

53

WO #91/17148
pub. 14 Nov 91

54

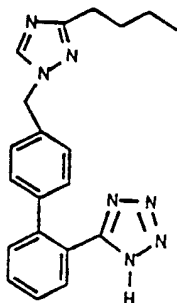
WO #91/17148
pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

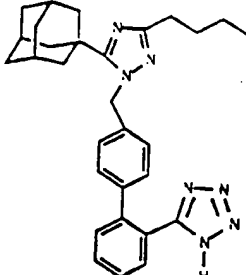
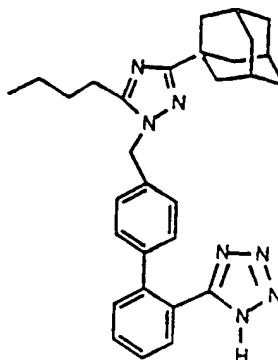
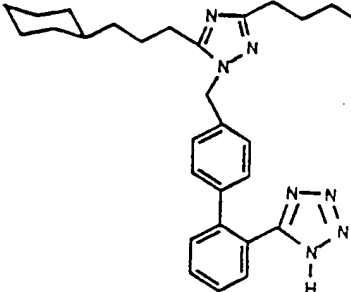
Compound #	Structure	Source
55		WO #91/17148 pub. 14 Nov 91
56		WO #91/17148 pub. 14 Nov 91
57		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

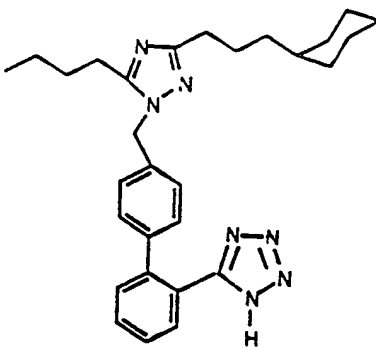
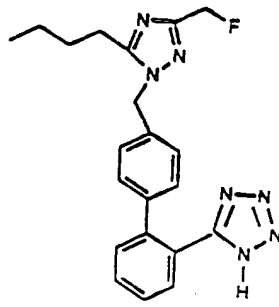
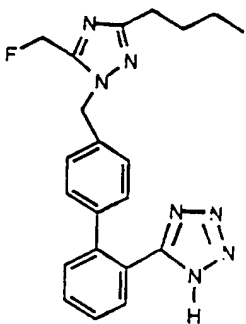
Compound #	Structure	Source
58		WO #91/17148 pub. 14 Nov 91
59		WO #91/17148 pub. 14 Nov 91
60		WO #91/17148 pub. 14 Nov 91

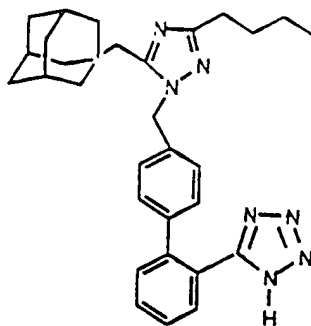
TABLE II: Angiotensin II Antagonists

Compound #

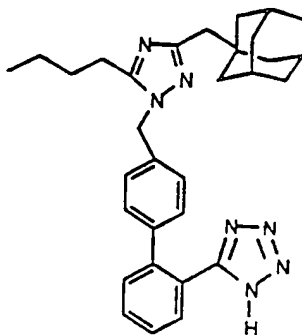
Structure

Source

61

WO #91/17148
pub. 14 Nov 91

62

WO #91/17148
pub. 14 Nov 91

63

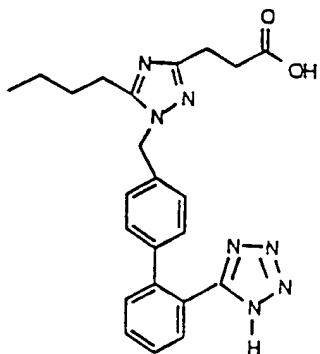
WO #91/17148
pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

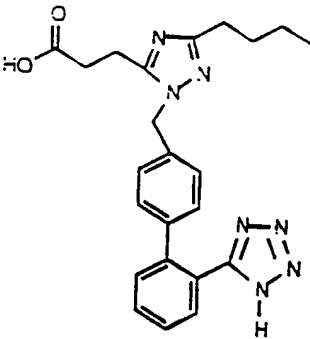
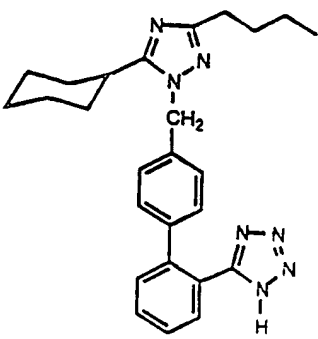
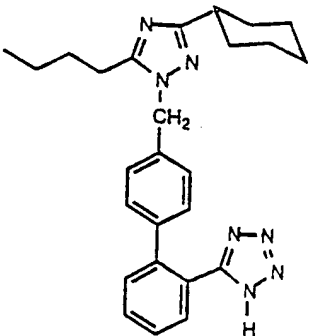
Compound #	Structure	Source
64		WO #91/17148 pub. 14 Nov 91
65		WO #91/17148 pub. 14 Nov 91
66		WO #91/17148 pub. 14 Nov 91

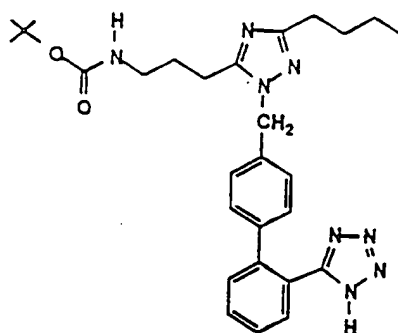
TABLE II: Angiotensin II Antagonists

Compound #

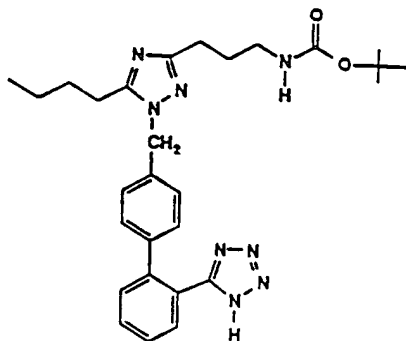
Structure

Source

67

WO #91/17148
pub. 14 Nov 91

68

WO #91/17148
pub. 14 Nov 91

69

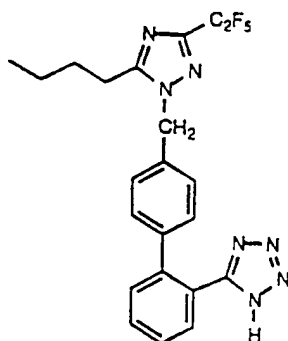
WO #91/17148
pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
70	 <chem>CCCC1=NC(C(F)(F)F)=NC(C1Cc2ccc(cc2)-c3ccccc3c4nn[nH]4)N</chem>	WO #91/17148 pub. 14 Nov 91
71	 <chem>CCCN1=NC(C)=[N+]([O-])C(C1Cc2ccc(cc2)-c3ccccc3c4nn[nH]4)N</chem>	WO #91/17148 pub. 14 Nov 91
72	 <chem>CCCN1=NC(C)=[N+]([O-])C(C1Cc2ccc(cc2)-c3ccccc3c4nn[nH]4)N</chem>	WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

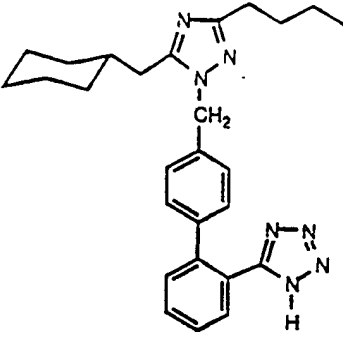
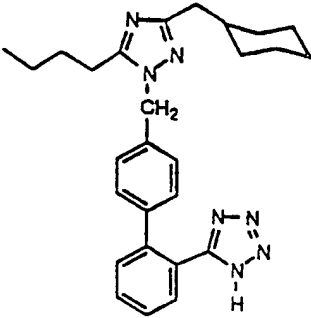
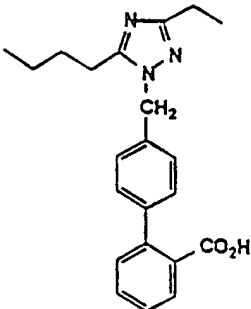
Compound #	Structure	Source
73		WO #91/17148 pub. 14 Nov 91
74		WO #91/17148 pub. 14 Nov 91
75		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

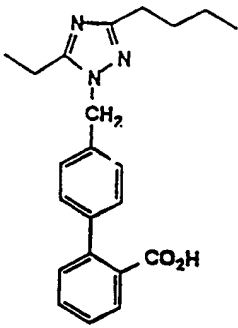
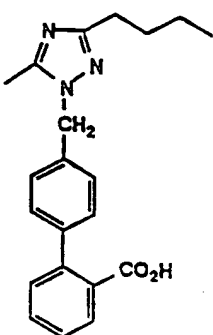
Compound #	Structure	Source
76		WO #91/17148 pub. 14 Nov 91
77		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

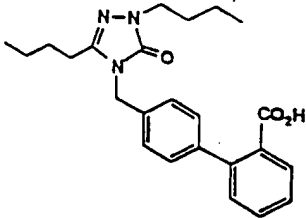
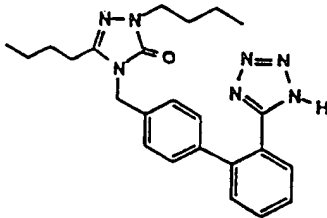
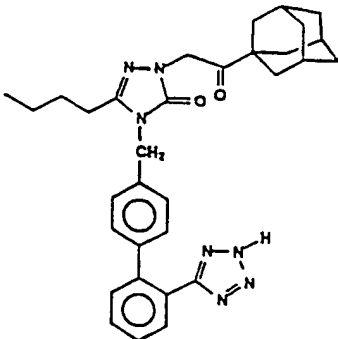
Compound #	Structure	Source
78		WO #91/18888 pub.
79		WO #91/18888 pub.
80		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

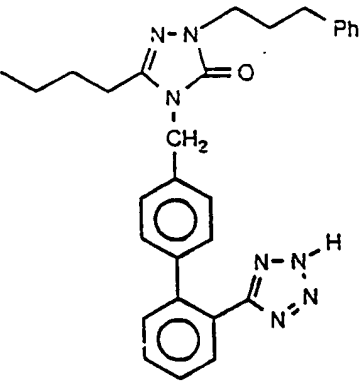
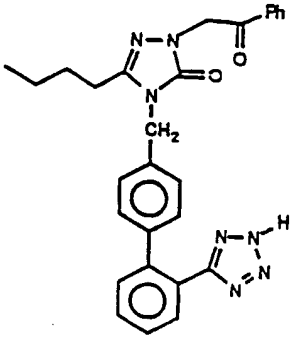
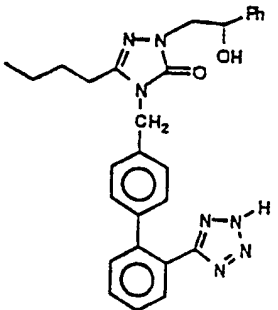
Compound #	Structure	Source
81		WO #91/18888 pub.
82		WO #91/18888 pub.
83		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

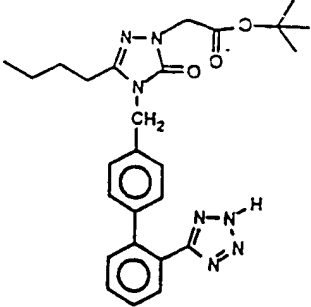
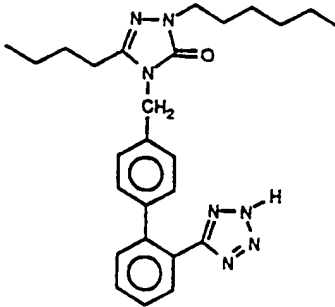
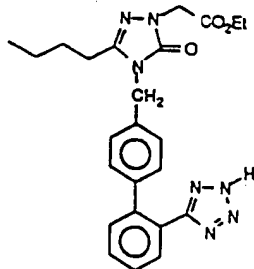
Compound #	Structure	Source
84		WO #91/18888 pub.
85		WO #91/18888 pub.
86		WO #91/18888 pub.

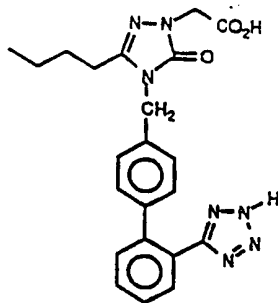
TABLE II: Angiotensin II Antagonists

Compound #

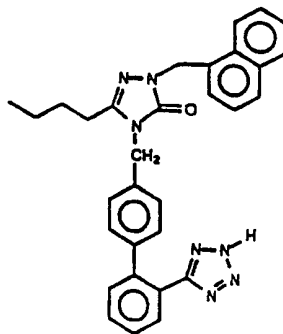
Structure

Source

87

WO #91/18888
pub.

88

WO #91/18888
pub.

89

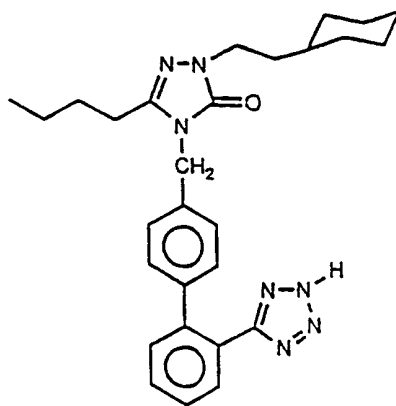
WO #91/18888
pub.

TABLE II: Angiotensin II Antagonists

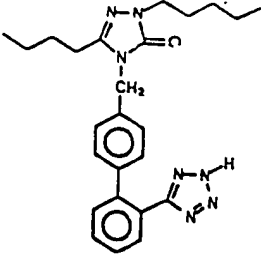
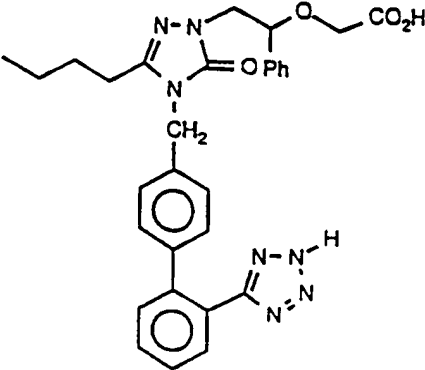
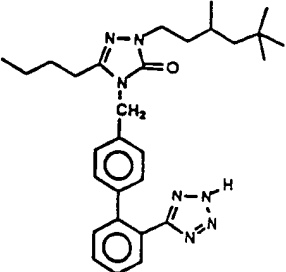
Compound #	Structure	Source
90		WO #91/18888 pub.
91		WO #91/18888 pub.
92		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

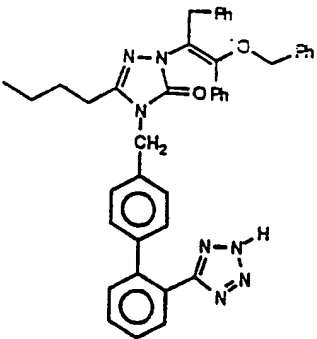
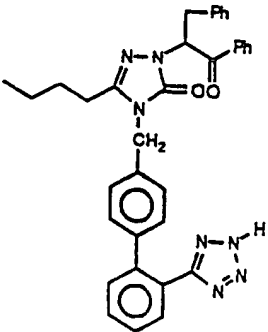
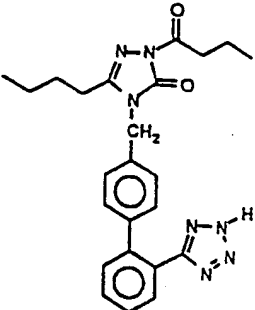
Compound #	Structure	Source
93		WO #91/18888 pub.
94		WO #91/18888 pub.
95		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

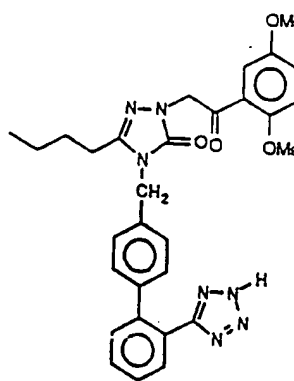
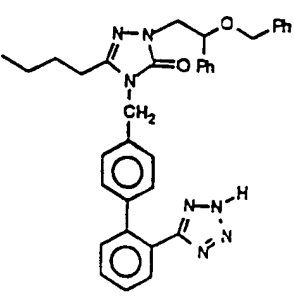
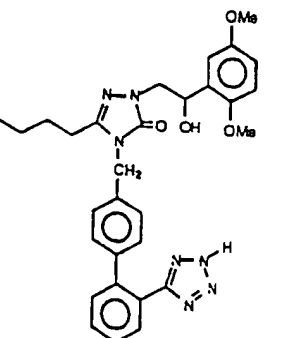
Compound #	Structure	Source
96		WO #91/18888 pub.
97		WO #91/18888 pub.
98		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

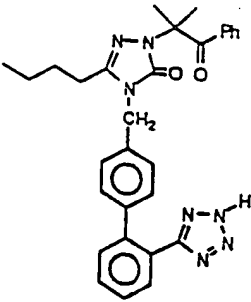
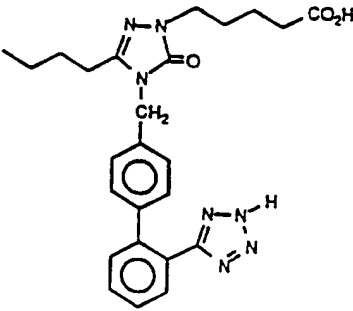
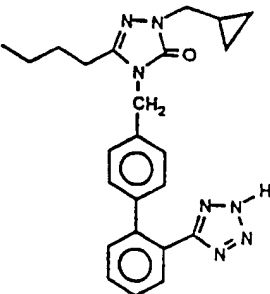
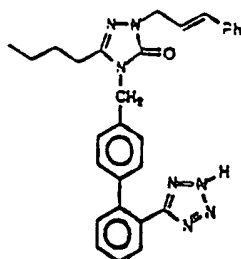
Compound #	Structure	Source
102		WO #91/18888 pub.
103		WO #91/18888 pub.
104		WO #91/18888 pub.

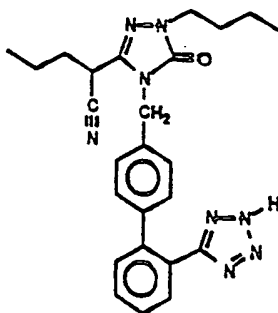
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

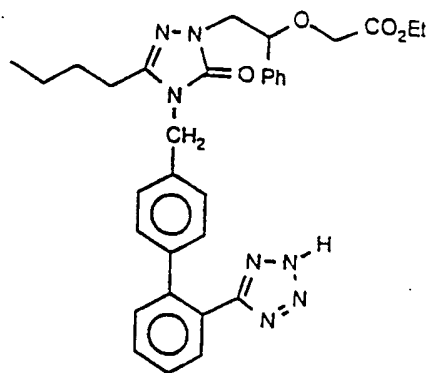
105

WO #91/18888
pub.

106

WO #91/18888
pub.

107

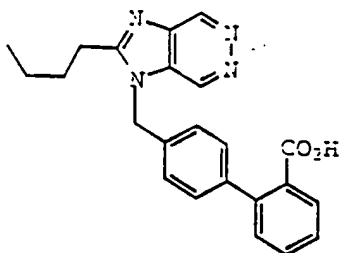
WO #91/18888
pub.

61

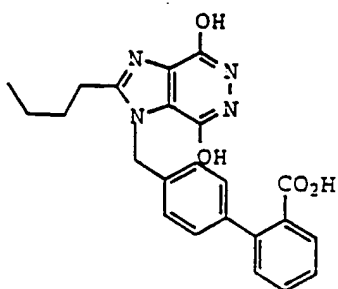
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

108

WO #91/19715
pub. 26 Dec 91

109

WO #91/19715
pub. 26 Dec 91

110

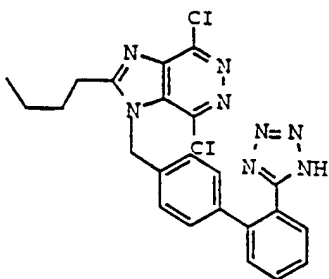
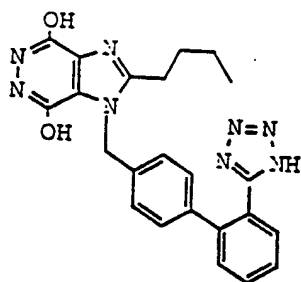
WO #91/19715
pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

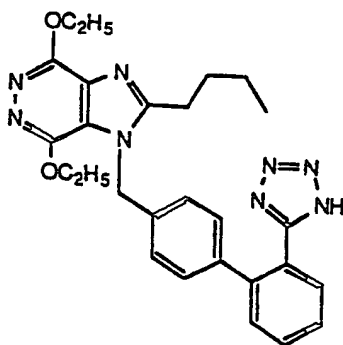
Compound #	Structure	Source
------------	-----------	--------

111



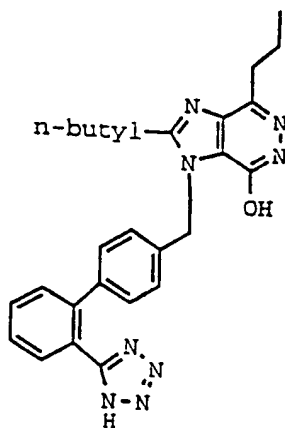
WO #91/19715
pub. 26 Dec 91

112



WO #91/19715
pub. 26 Dec 91

113

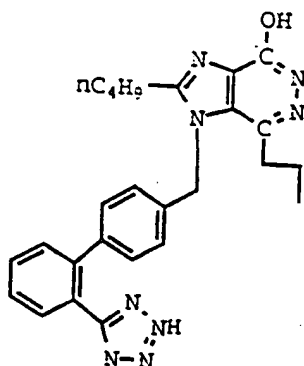


WO #91/19715
pub. 26 Dec 91

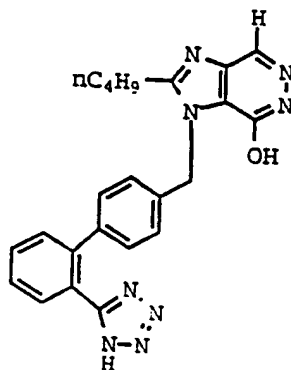
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

114

WO #91/19715
pub. 26 Dec 91

115

WO #91/19715
pub. 26 Dec 91

116

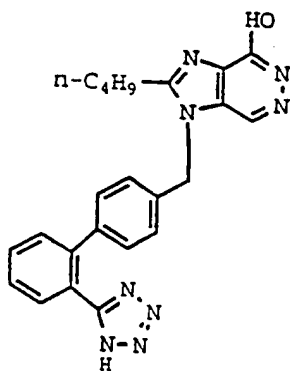
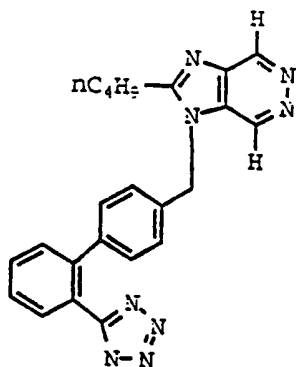
WO #91/19715
pub. 26 Dec 91

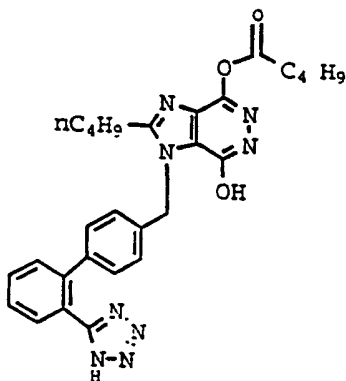
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

117

WO #91/19715
pub. 26 Dec 91

118

WO #91/19715
pub. 26 Dec 91

119

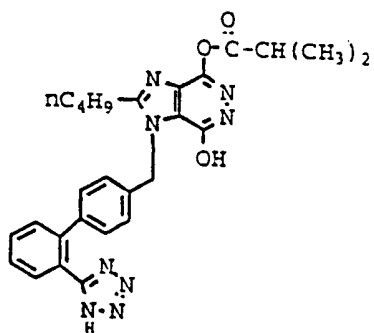
WO #91/19715
pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

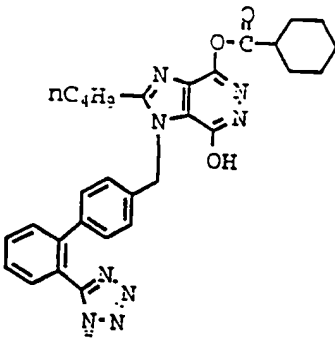
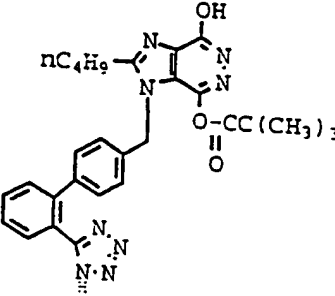
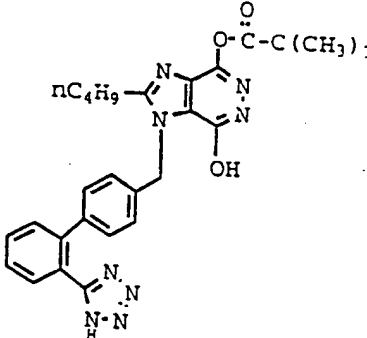
Compound #	Structure	Source
120		WO #91/19715 pub. 26 Dec 91
121		WO #91/19715 pub. 26 Dec 91
122		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

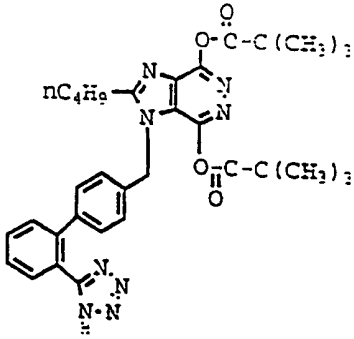
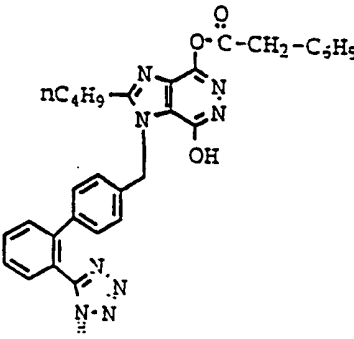
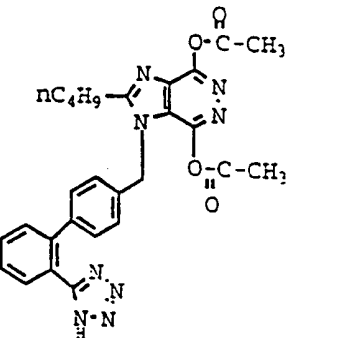
Compound #	Structure	Source
123		WO #91/19715 pub. 26 Dec 91
124		WO #91/19715 pub. 26 Dec 91
125		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

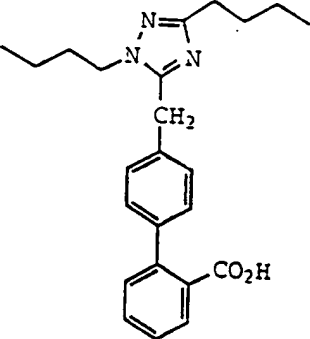
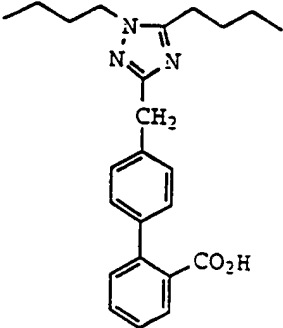
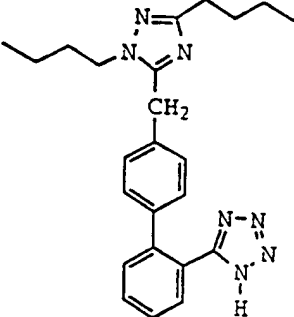
Compound #	Structure	Source
126		WO #92/05161 pub. 2 Apr 92
127		WO #92/05161 pub. 2 Apr 92
128		WO #92/05161 pub. 2 Apr 92

TABLE II: Angiotensin II Antagonists

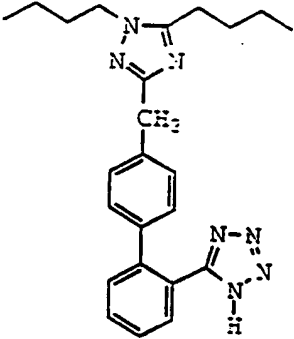
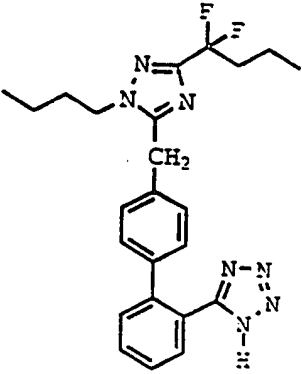
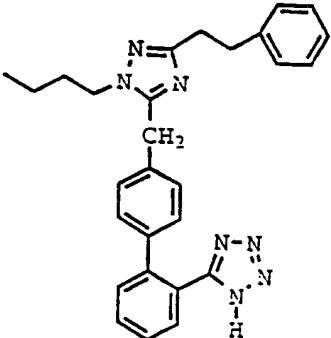
Compound #	Structure	Source
129		WO #92/05161 pub. 2 Apr 92
130		WO #92/05161 pub. 2 Apr 92
131		WO #92/05161 pub. 2 Apr 92

TABLE II: Angiotensin II Antagonists

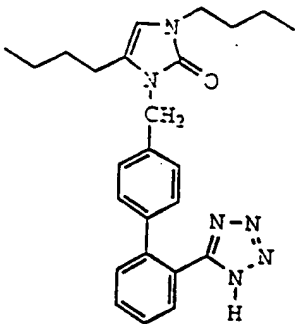
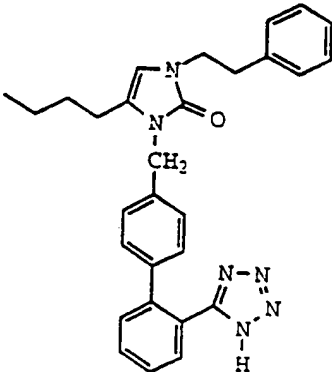
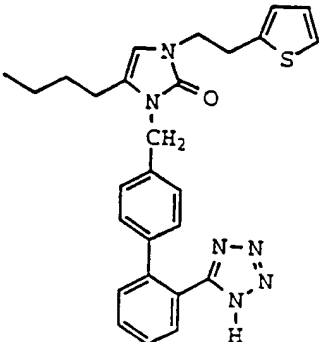
Compound #	Structure	Source
132		WO #92/07834 pub. 14 May 92
133		WO #92/07834 pub. 14 May 92
134		WO #92/07834 pub. 14 May 92

TABLE II: Angiotensin II Antagonists

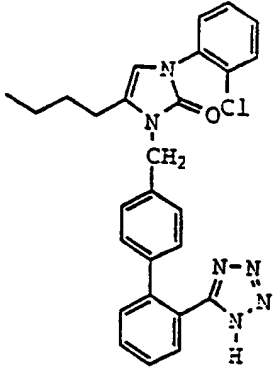
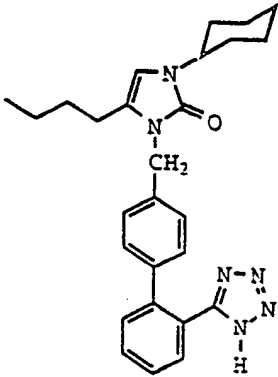
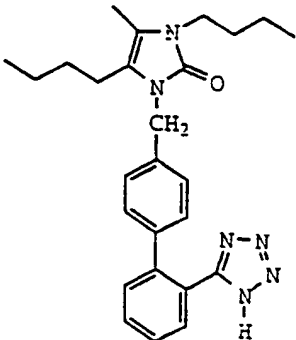
Compound #	Structure	Source
135		WO #92/07834 pub. 14 May 92
136		WO #92/07834 pub. 14 May 92
137		WO #92/07834 pub. 14 May 92

TABLE II: Angiotensin II Antagonists

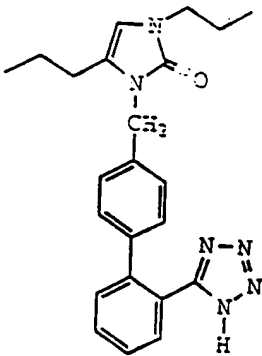
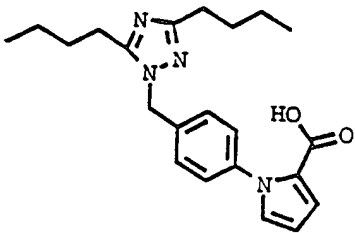
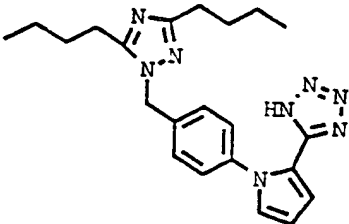
Compound #	Structure	Source
138		WO #92/07834 pub. 14 May 92
139		WO #92/11255 pub. 9 Jul 92
140		WO #92/11255 pub. 9 Jul 92

TABLE II: Angiotensin II Antagonists

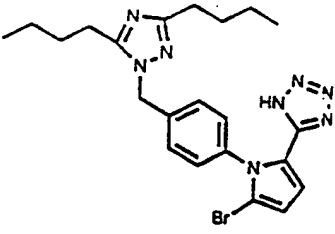
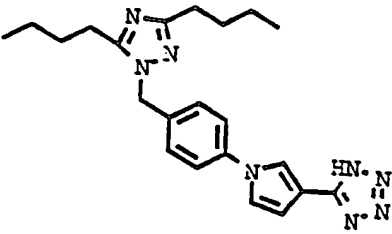
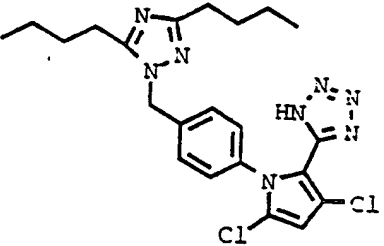
Compound #	Structure	Source
141		WO #92/11255 pub. 9 Jul 92
142		WO #92/11255 pub. 9 Jul 92
143		WO #92/11255 pub. 9 Jul 92

TABLE II: Angiotensin II Antagonists

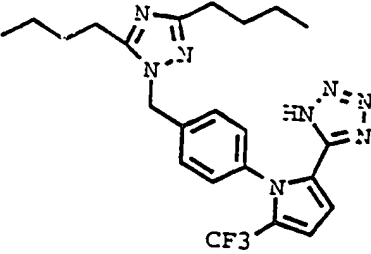
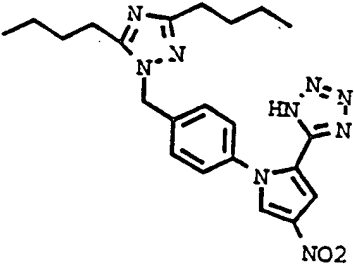
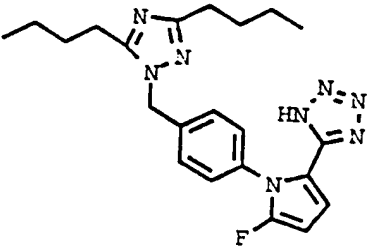
Compound #	Structure	Source
144		WO #92/11255 pub. 9 Jul 92
145		WO #92/11255 pub. 9 Jul 92
146		WO #92/11255 pub. 9 Jul 92

TABLE II: Angiotensin II Antagonists

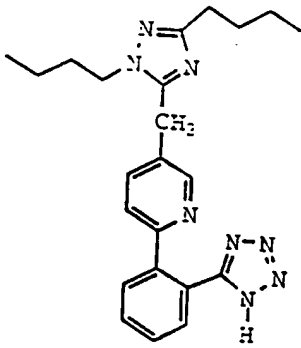
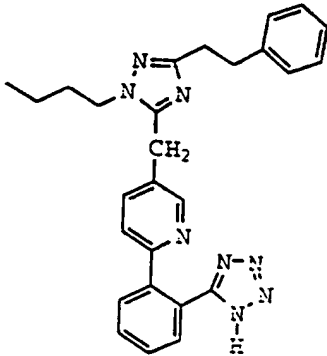
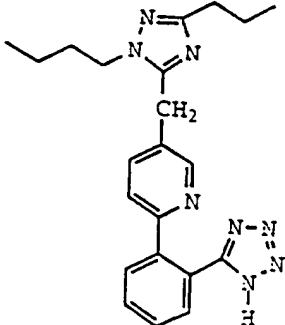
Compound #	Structure	Source
150		WO #92/16523 pub. 1 Oct 92
151		WO #92/16523 pub. 1 Oct 92
152		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

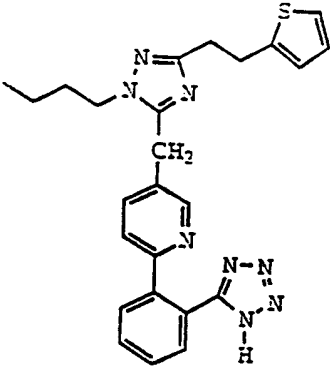
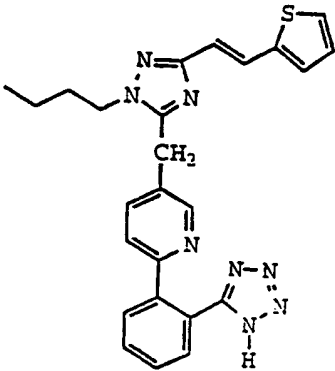
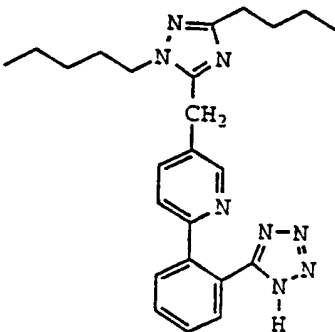
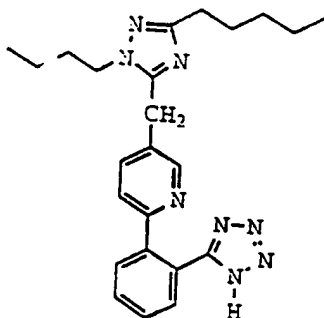
Compound #	Structure	Source
153		WO #92/16523 pub. 1 Oct 92
154		WO #92/16523 pub. 1 Oct 92
155		WO #92/16523 pub. 1 Oct 92

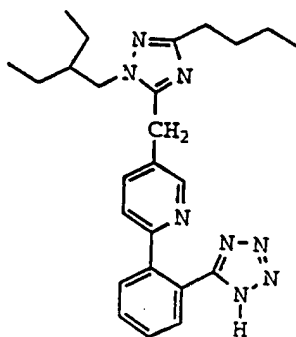
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

156

WO #92/16523
pub. 1 Oct 92

157

WO #92/16523
pub. 1 Oct 92

158

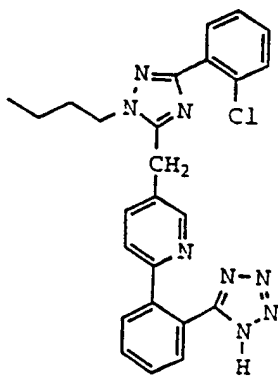
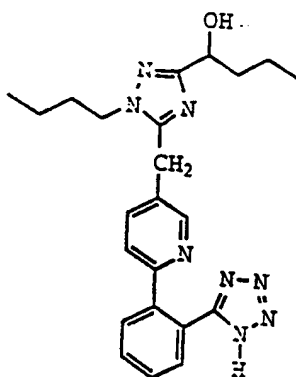
WO #92/16523
pub. 1 Oct 92

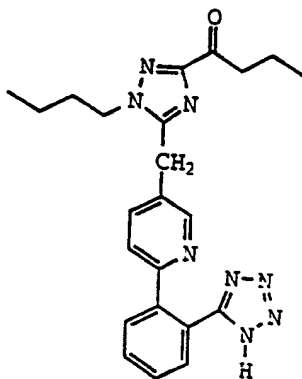
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

159

WO #92/16523
pub. 1 Oct 92

160

WO #92/16523
pub. 1 Oct 92

161

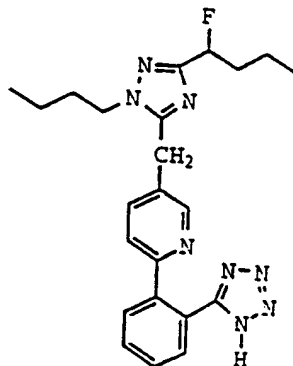
WO #92/16523
pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

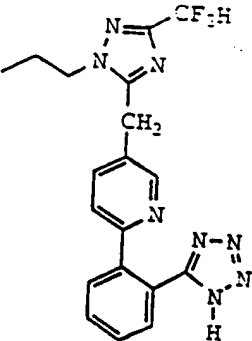
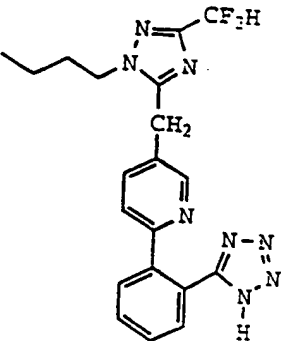
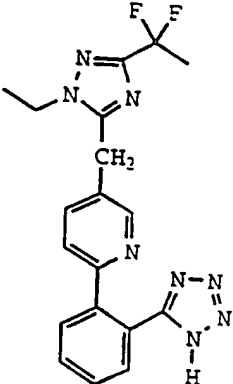
Compound #	Structure	Source
162		WO #92/16523 pub. 1 Oct 92
163		WO #92/16523 pub. 1 Oct 92
164		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

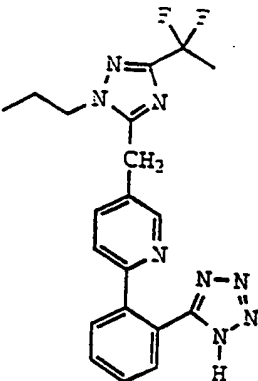
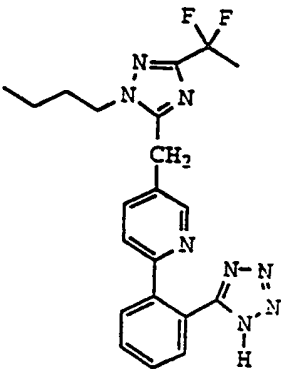
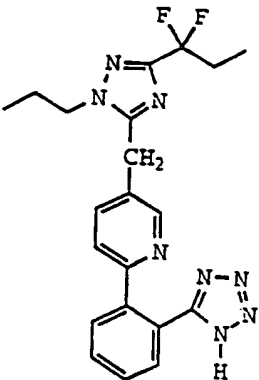
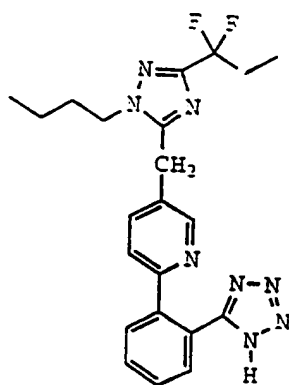
Compound #	Structure	Source
165		WO #92/16523 pub. 1 Oct 92
166		WO #92/16523 pub. 1 Oct 92
167		WO #92/16523 pub. 1 Oct 92

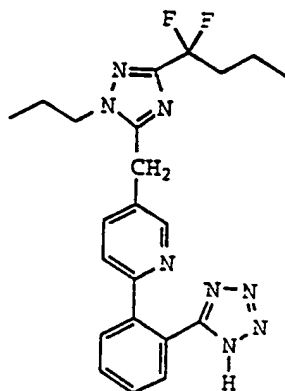
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

168

WO #92/16523
pub. 1 Oct 92

169

WO #92/16523
pub. 1 Oct 92

170

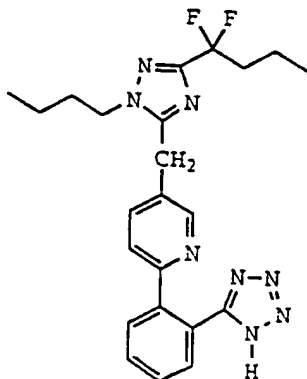
WO #92/16523
pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

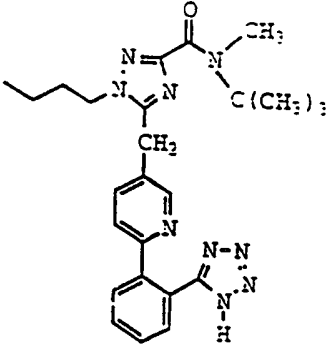
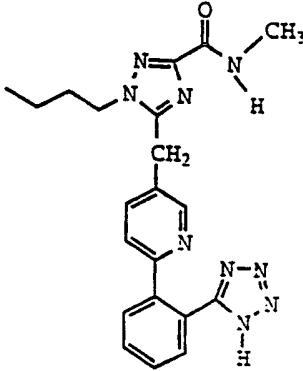
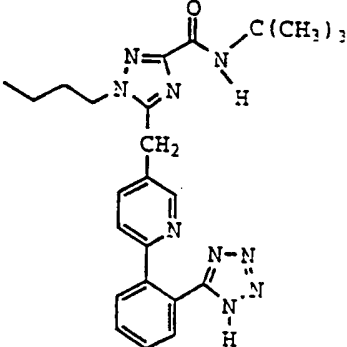
Compound #	Structure	Source
171		WO #92/16523 pub. 1 Oct 92
172		WO #92/16523 pub. 1 Oct 92
173		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
177	 <chem>CCCCN1C=NC(C1Cc2ccc3c(c2)c(cnn3)C4=NN=CN4)C(=O)OCC</chem>	WO #92/16523 pub. 1 Oct 92
178	 <chem>CCCCN1C=NC(C1Cc2ccc3c(c2)c(cnn3)C4=NN=CN4)C(=O)OCC(C)C</chem>	WO #92/16523 pub. 1 Oct 92
179	 <chem>CCCCN1C=NC(C1Cc2ccc3c(c2)c(cnn3)C4=NN=CN4)C=O</chem>	WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

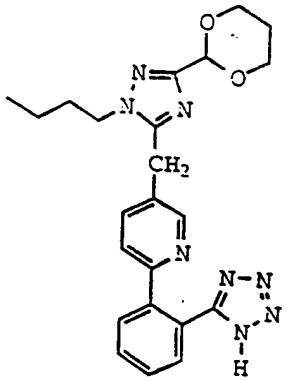
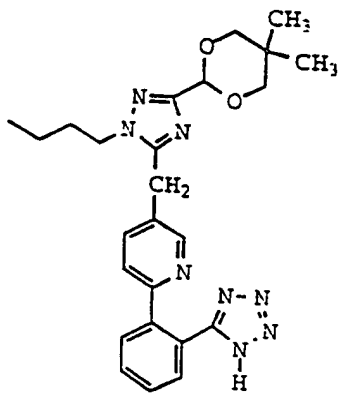
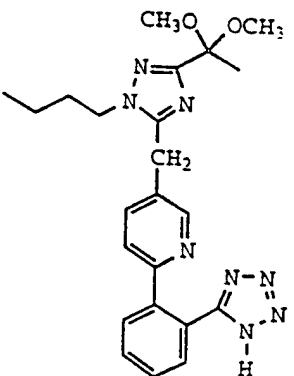
Compound #	Structure	Source
180		WO #92/16523 pub. 1 Oct 92
181		WO #92/16523 pub. 1 Oct 92
182		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

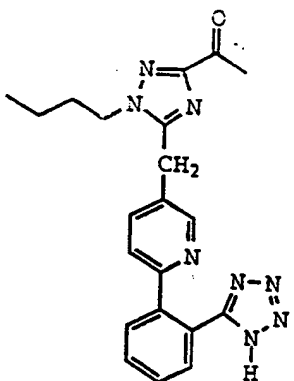
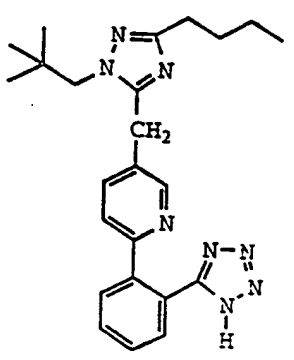
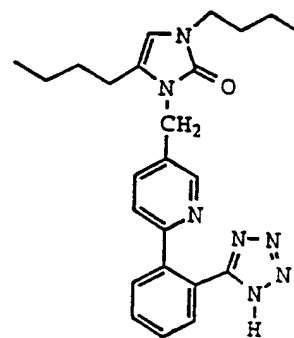
Compound #	Structure	Source
183		WO #92/16523 pub. 1 Oct 92
184		WO #92/16523 pub. 1 Oct 92
185		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

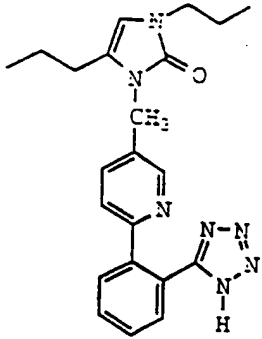
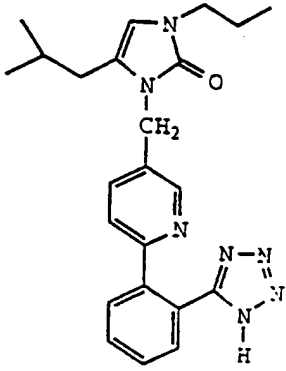
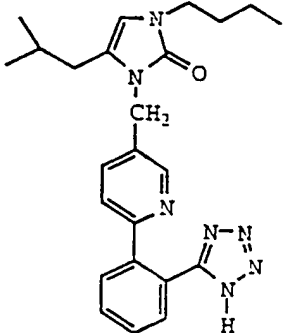
Compound #	Structure	Source
186		WO #92/17469 pub. 15 Oct 92
187		WO #92/17469 pub. 15 Oct 92
188		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

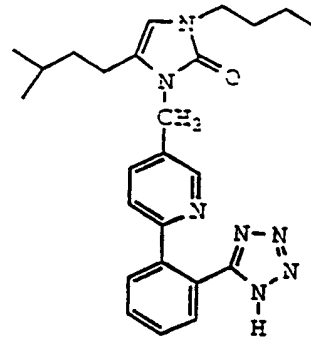
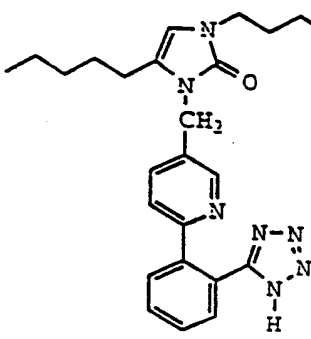
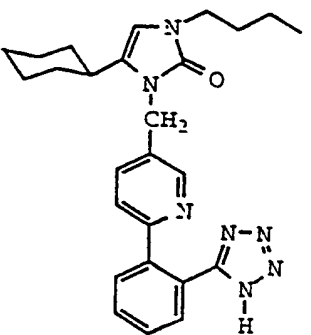
Compound #	Structure	Source
189		WO #92/17469 pub. 15 Oct 92
190		WO #92/17469 pub. 15 Oct 92
191		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

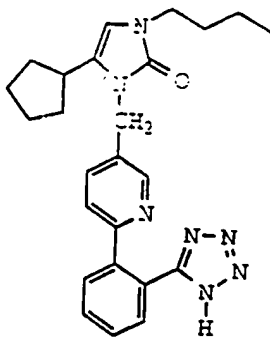
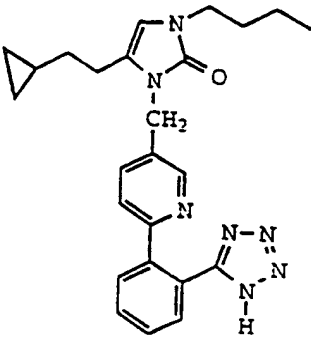
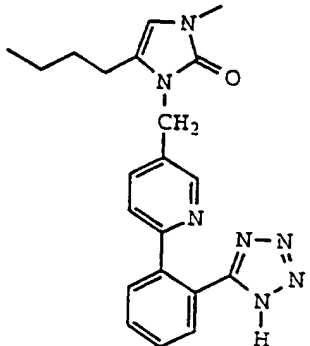
Compound #	Structure	Source
192		WO #92/17469 pub. 15 Oct 92
193		WO #92/17469 pub. 15 Oct 92
194		WO #92/17469 pub. 15 Oct 92

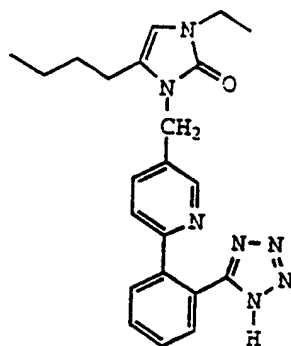
TABLE II: Angiotensin II Antagonists

Compound #

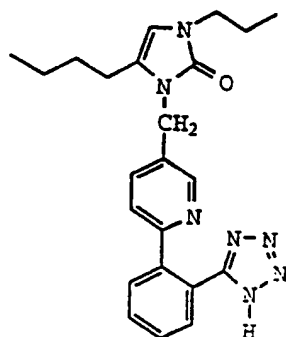
Structure

Source

195

WO #92/17469
pub. 15 Oct 92

196

WO #92/17469
pub. 15 Oct 92

197

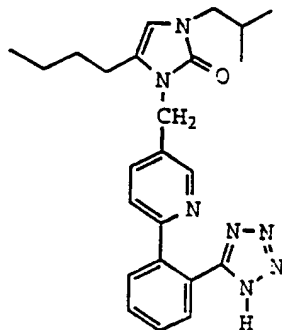
WO #92/17469
pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

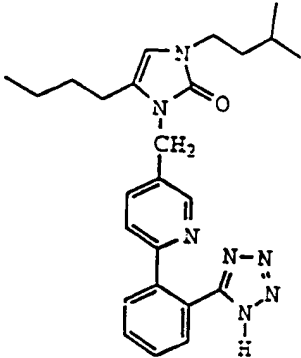
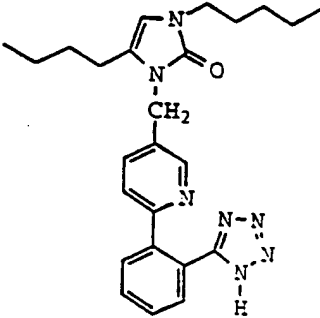
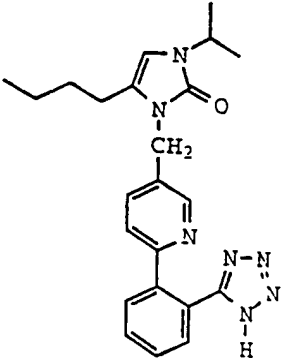
Compound #	Structure	Source
198		WO #92/17469 pub. 15 Oct 92
199		WO #92/17469 pub. 15 Oct 92
200		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

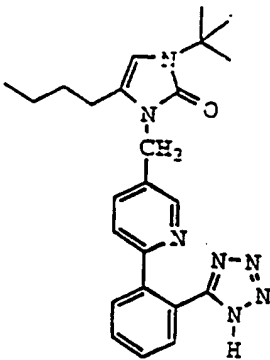
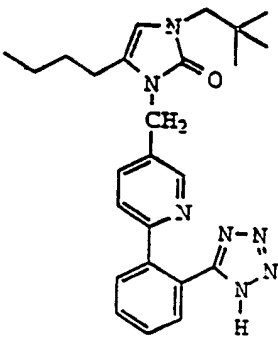
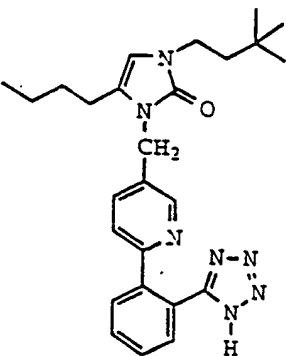
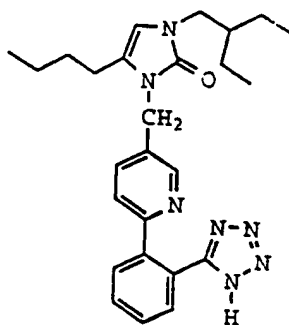
Compound #	Structure	Source
201		WO #92/17469 pub. 15 Oct 92
202		WO #92/17469 pub. 15 Oct 92
203		WO #92/17469 pub. 15 Oct 92

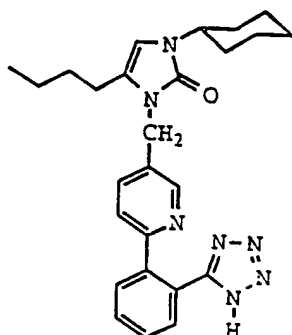
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

204

WO #92/17469
pub. 15 Oct 92

205

WO #92/17469
pub. 15 Oct 92

206

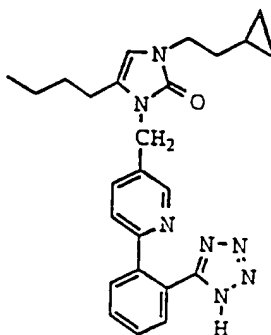
WO #92/17469
pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

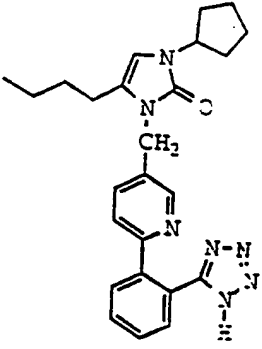
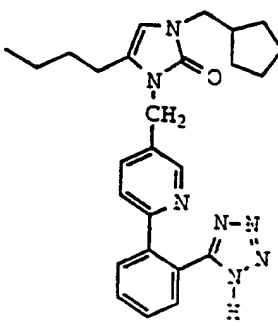
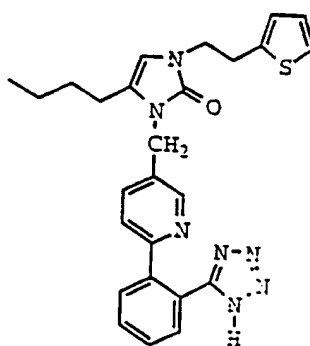
Compound #	Structure	Source
207		WO #92/17469 pub. 15 Oct 92
208		WO #92/17469 pub. 15 Oct 92
209		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

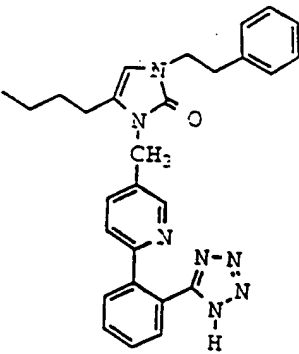
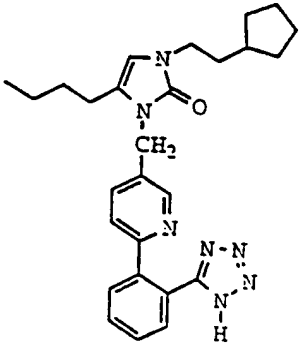
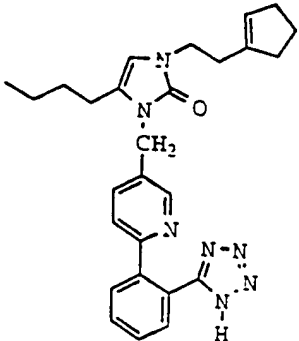
Compound #	Structure	Source
210		WO #92/17469 pub. 15 Oct 92
211		WO #92/17469 pub. 15 Oct 92
212		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

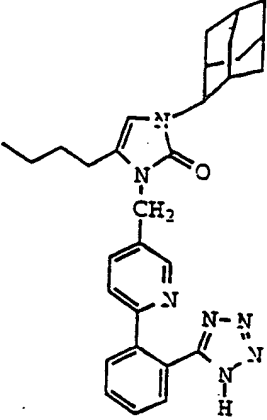
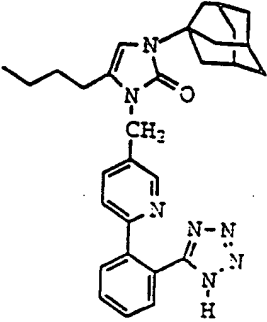
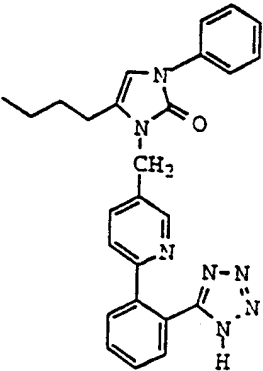
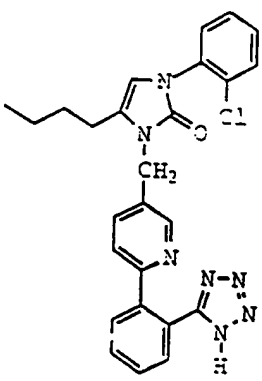
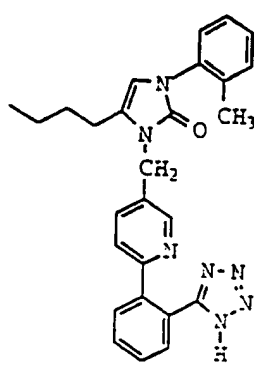
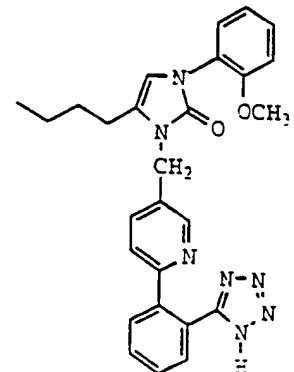
Compound #	Structure	Source
213		WO #92/17469 pub. 15 Oct 92
214		WO #92/17469 pub. 15 Oct 92
215		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

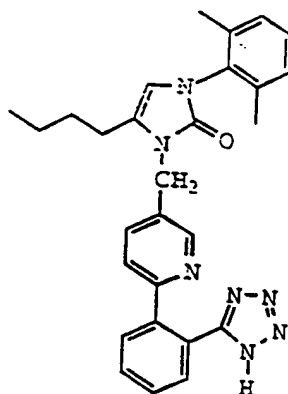
Compound #	Structure	Source
216		WO #92/17469 pub. 15 Oct 92
217		WO #92/17469 pub. 15 Oct 92
218		WO #92/17469 pub. 15 Oct 92

Compound #	Structure	Source
219		WO #92/17469 pub. 15 Oct 92
220		WO #92/17469 pub. 15 Oct 92
221		WO #92/17469 pub. 15 Oct 92

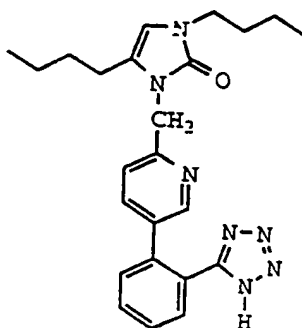
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

222

WO #92/17469
pub. 15 Oct 92

223

WO #92/17469
pub. 15 Oct 92

224

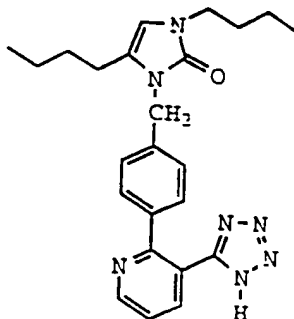
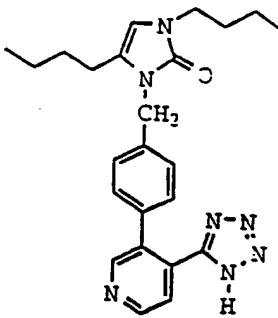
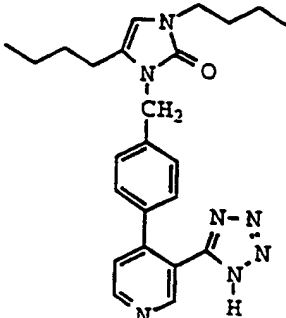
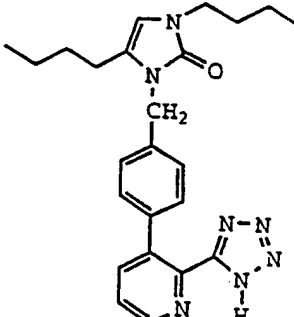
WO #92/17469
pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

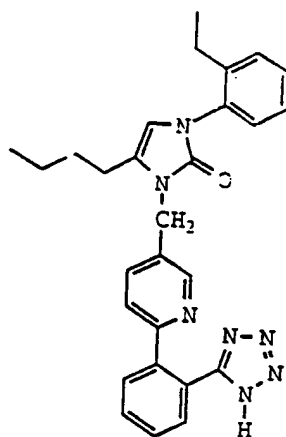
Compound #	Structure	Source
225		WO #92/17469 pub. 15 Oct 92
226		WO #92/17469 pub. 15 Oct 92
227		WO #92/17469 pub. 15 Oct 92

101

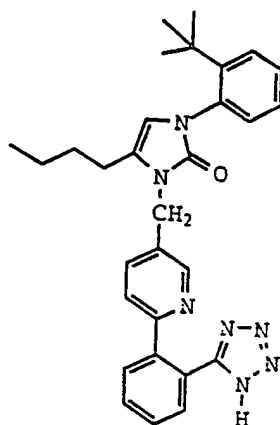
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

228



229



230

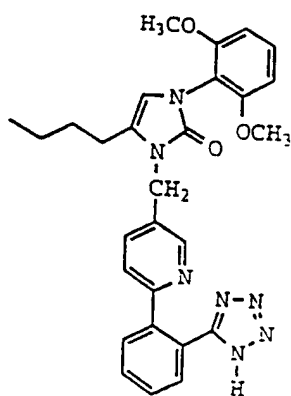
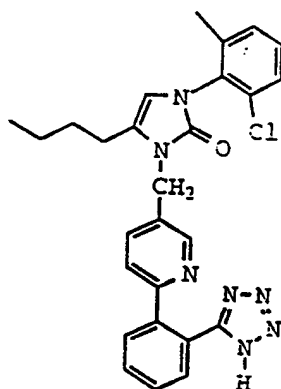


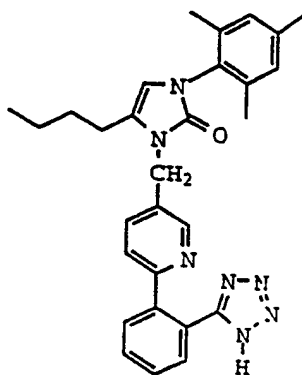
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

231



232



233

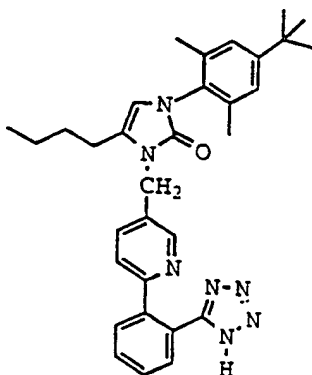
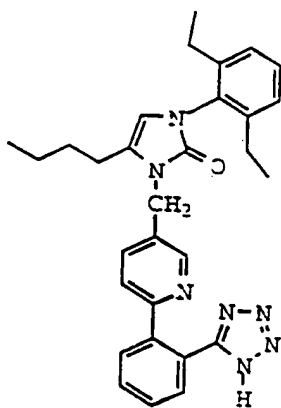


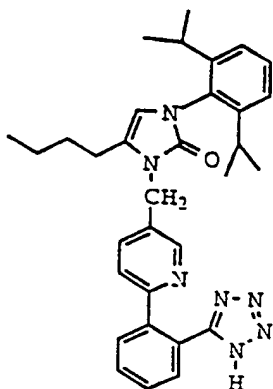
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

234



235



236

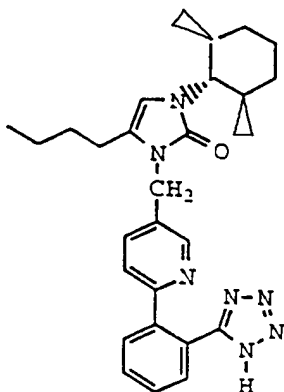


TABLE II: Angiotensin II Antagonists

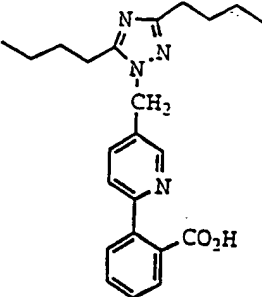
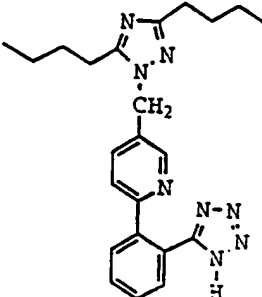
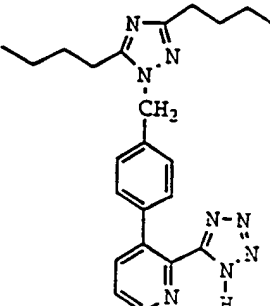
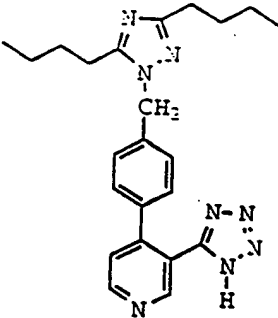
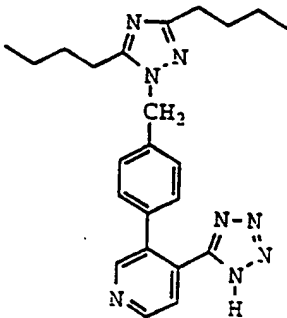
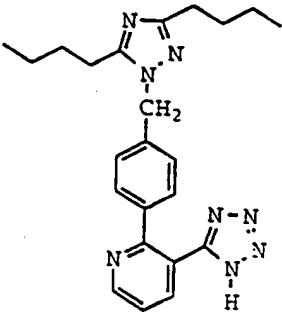
Compound #	Structure	Source
240		WO #92/18092 pub. 29 Oct 92
241		WO #92/18092 pub. 29 Oct 92
242		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
243		WO #92/18092 pub. 29 Oct 92
244		WO #92/18092 pub. 29 Oct 92
245		WO #92/18092 pub. 29 Oct 92

107

TABLE II: Angiotensin II Antagonists

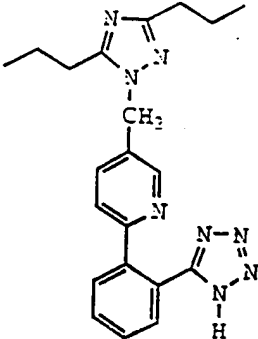
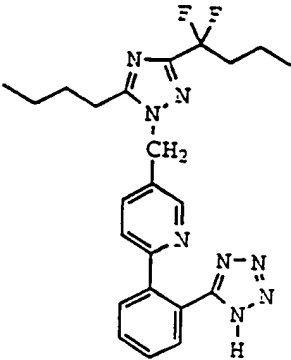
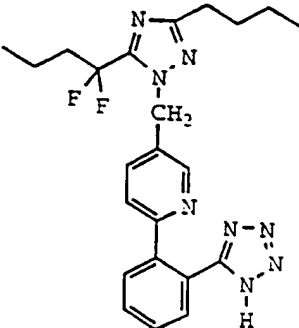
Compound #	Structure	Source
246		WO #92/18092 pub. 29 Oct 92
247		WO #92/18092 pub. 29 Oct 92
248		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

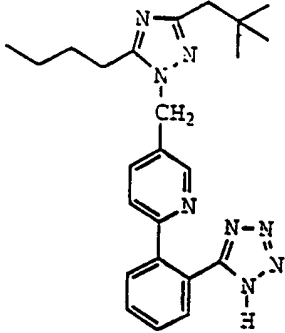
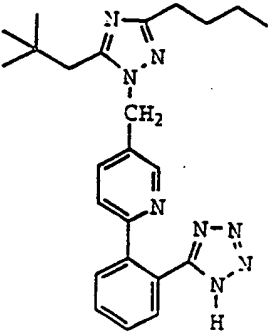
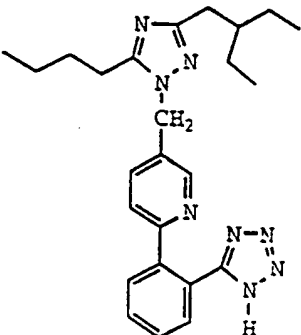
Compound #	Structure	Source
249		WO #92/18092 pub. 29 Oct 92
250		WO #92/18092 pub. 29 Oct 92
251		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

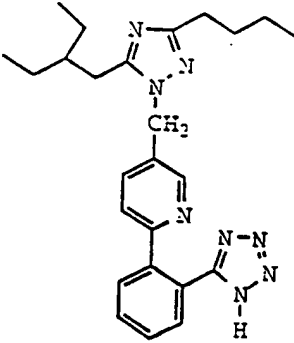
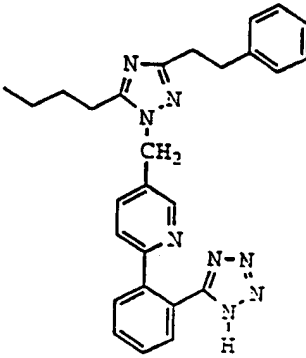
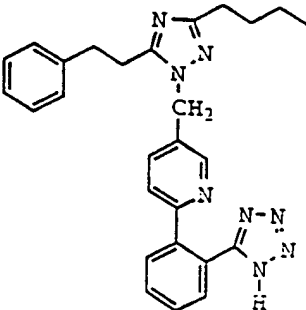
Compound #	Structure	Source
252		WO #92/18092 pub. 29 Oct 92
253		WO #92/18092 pub. 29 Oct 92
254		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

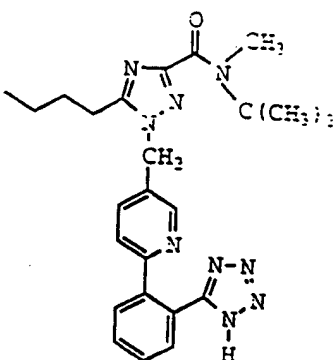
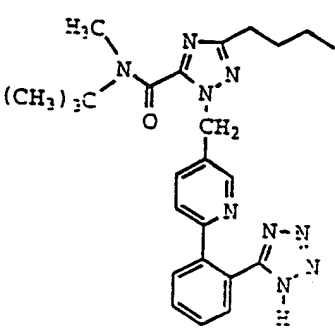
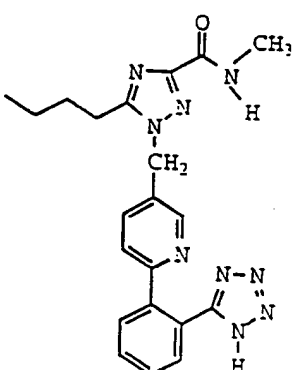
Compound #	Structure	Source
255		WO #92/18092 pub. 29 Oct 92
256		WO #92/18092 pub. 29 Oct 92
257		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

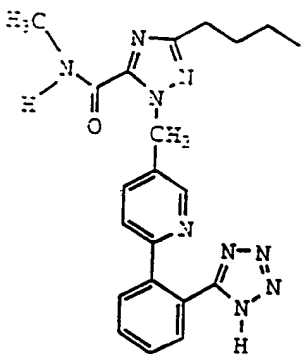
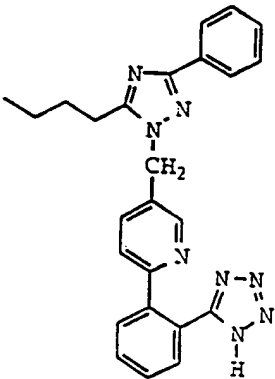
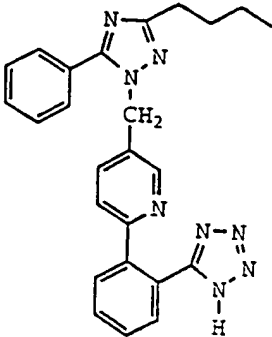
Compound #	Structure	Source
258		WO #92/18092 pub. 29 Oct 92
259		WO #92/18092 pub. 29 Oct 92
260		WO #92/18092 pub. 29 Oct 92

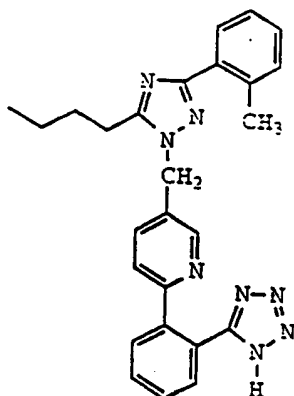
TABLE II: Angiotensin II Antagonists

Compound #

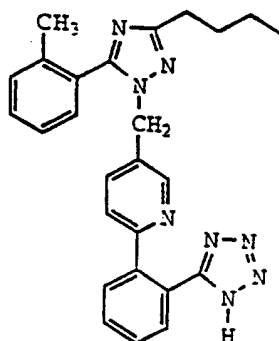
Structure

Source

261

WO #92/18092
pub. 29 Oct 92

262

WO #92/18092
pub. 29 Oct 92

263

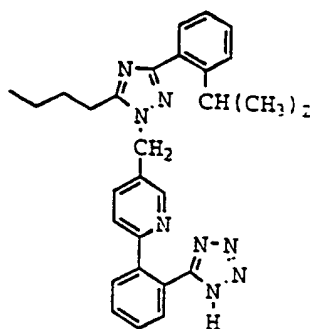
WO #92/18092
pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

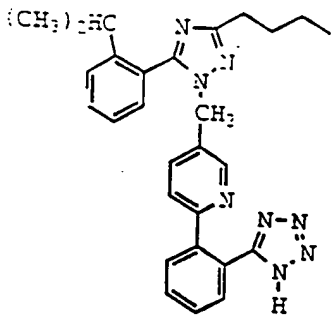
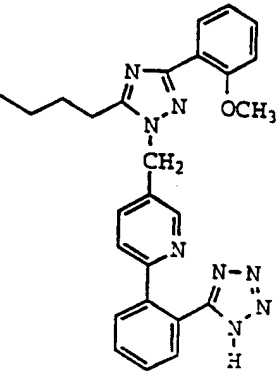
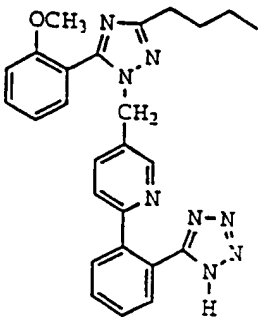
Compound #	Structure	Source
264		WO #92/18092 pub. 29 Oct 92
265		WO #92/18092 pub. 29 Oct 92
266		WO #92/18092 pub. 29 Oct 92

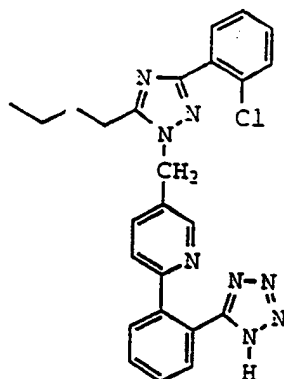
TABLE II: Angiotensin II Antagonists

Compound #

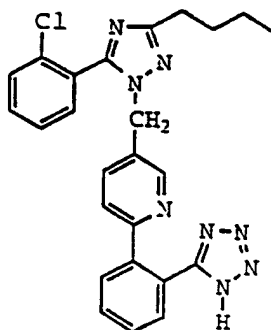
Structure

Source

267

WO #92/18092
pub. 29 Oct 92

268

WO #92/18092
pub. 29 Oct 92

269

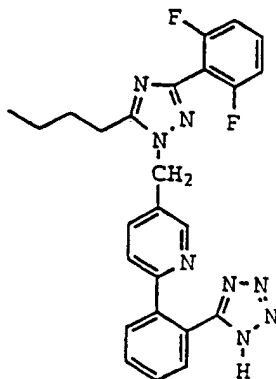
WO #92/18092
pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

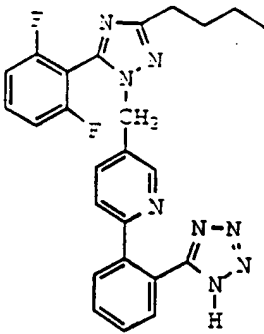
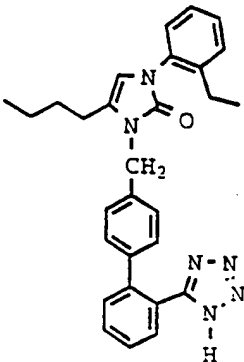
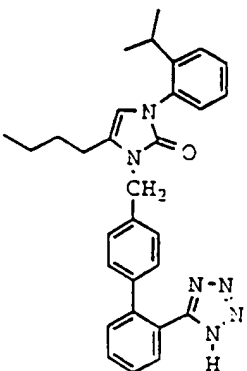
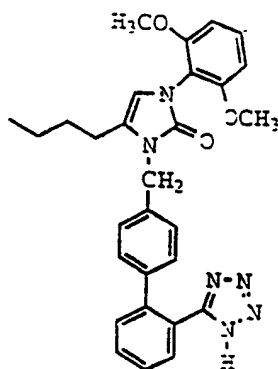
Compound #	Structure	Source
270		WO #92/18092 pub. 29 Oct 92
271		PCT/US95/02156 filed 8 Mar 94
272		PCT/US94/02156 filed 8 Mar 94

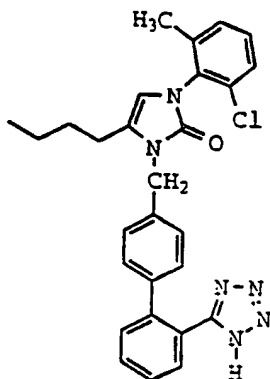
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

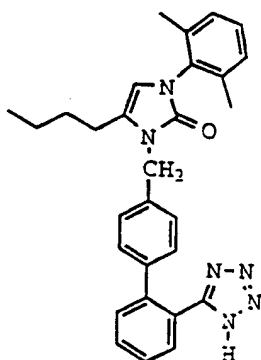
273

PCT/US94/02156
filed 8 Mar 94

274

PCT/US94/02156
filed 8 Mar 94

275

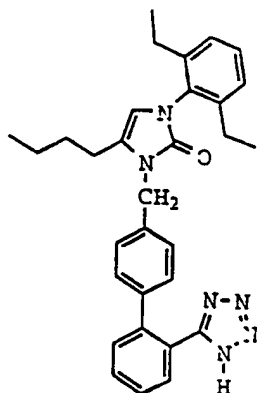
PCT/US94/02156
filed 8 Mar 94

117

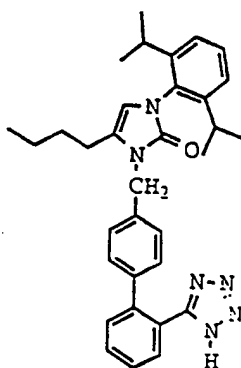
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

276

PCT/US94/02156
filed 8 Mar 94

277

PCT/US94/02156
filed 8 Mar 94

278

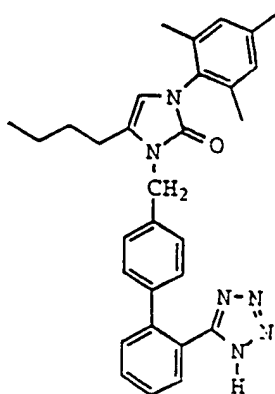
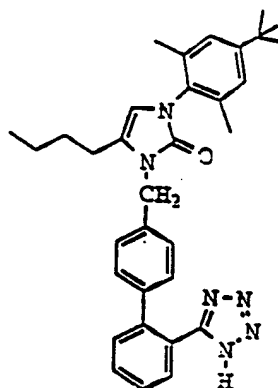
PCT/US94/02156
filed 8 Mar 94

TABLE II: Angiotensin II Antagonists

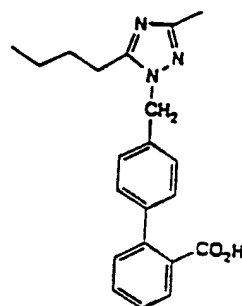
Compound #	Structure	Source
------------	-----------	--------

279



PCT/US94/02156
filed 8 Mar 94

280



WO #91/17148
pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

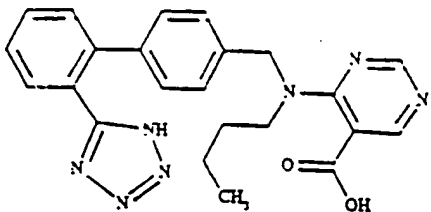
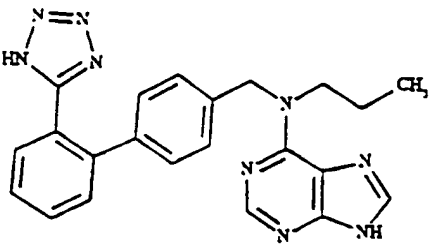
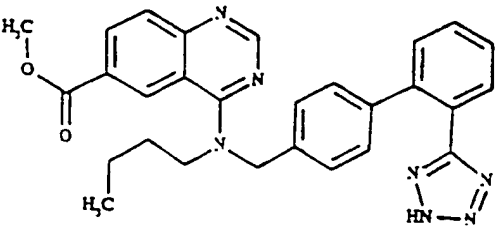
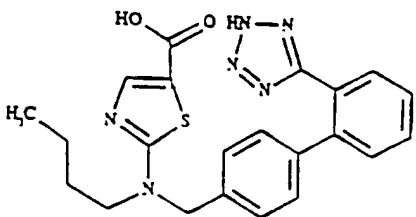
Compound #	Structure	Source
281		EP #475,206 pub. 18 Mar 92
282		WO #93/18035 pub. 16 Sep 93
283		WO #93/17628 pub. 16 Sep 93
284		WO #93/17681 pub. 16 Sep 93

TABLE II: Angiotensin II Antagonists

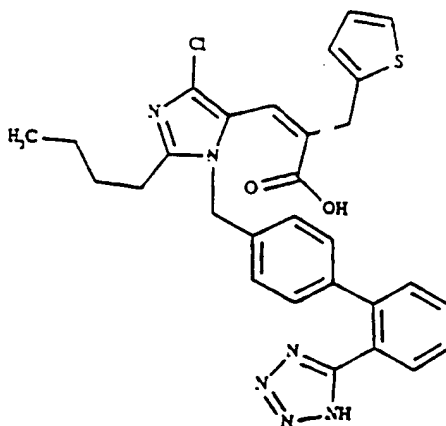
Compound #	Structure	Source
285	 <chem>CCCCC1=NC(Cl)=C(CO)N1Cc2ccc(cc2)CC3CCCC3C(=O)O</chem>	EP #513,533 pub. 19 Nov 92
286	 <chem>CCCCC1=NC(Cl)=C(CO)N1Cc2ccc(cc2)CC3CCCC3C(=O)O</chem>	EP #535,463 pub. 07 Apr 93
287	 <chem>CCCCC1=NC(Cl)=C(CO)N1Cc2ccc(cc2)CC3CCCC3C(=O)O</chem>	EP #535,465 pub. 07 Apr 93

121

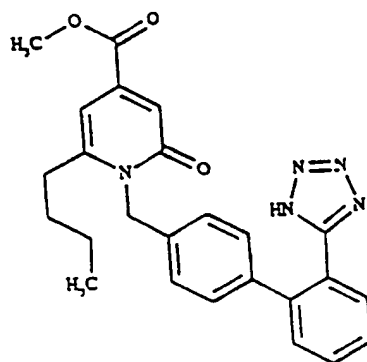
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

288

EP #539,713
pub. 05 May 93

289

EP #542,059
pub. 19 May 93

290

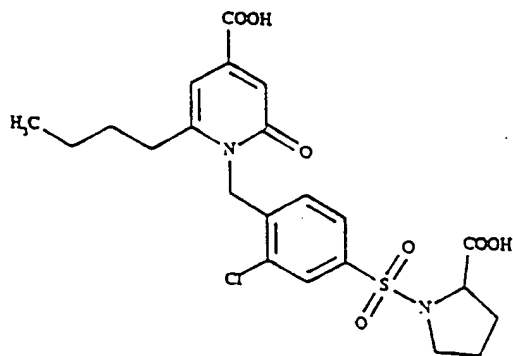
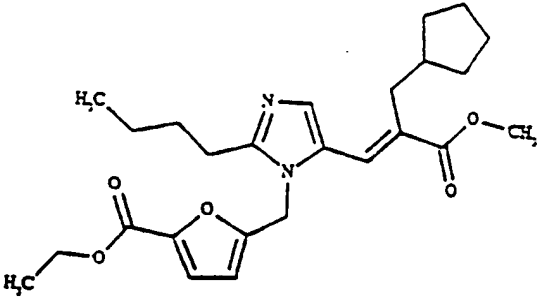
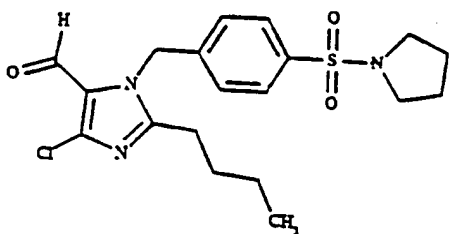
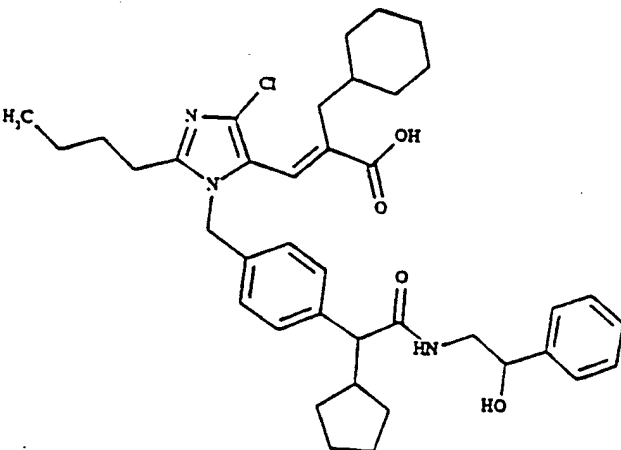
EP #05 557,843
pub. 01 Sep 93

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
291		EP #563,705 pub. 06 Oct 93
292		EP #562,261 pub. 29 Sep 93
293		EP #05 557,843 pub. 15 Sep 93

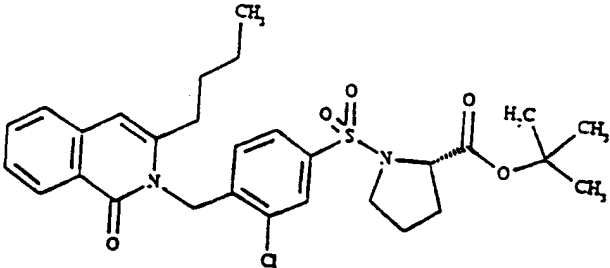
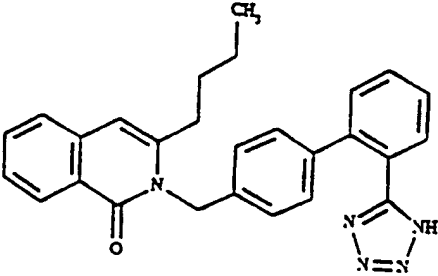
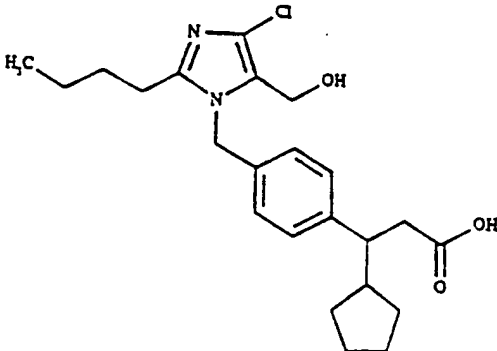
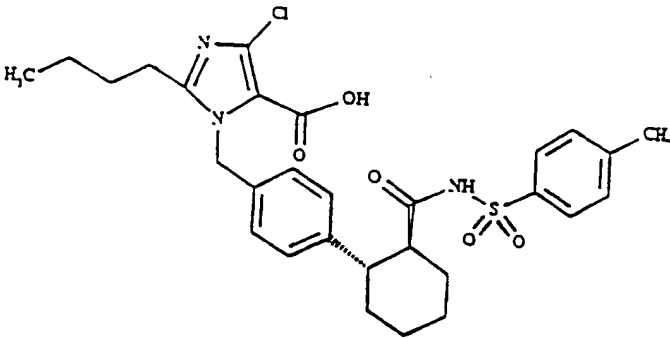
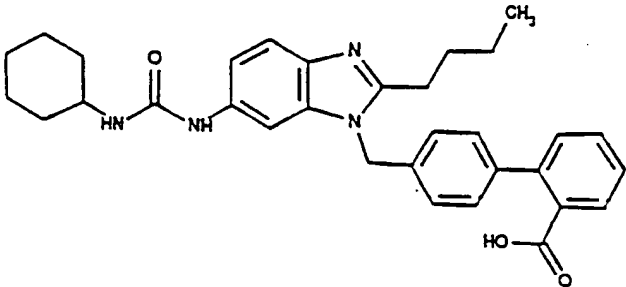
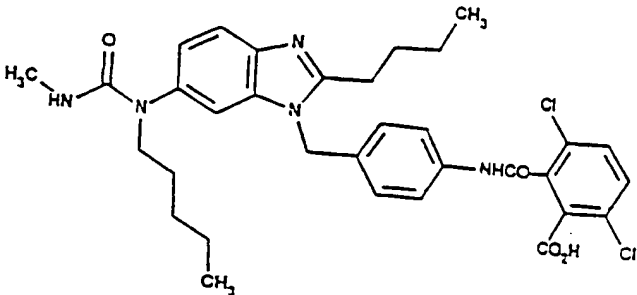
Compound #	Structure	Source
297		EP #0,569,795 pub. 18 Nov 93
298		EP #0,569,794 pub. 18 Nov 93
299		EP #0,578,002 pub. 12 Jan 94

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
300		EP #581,003 pub. 02 Feb 94
301		EP #392,317 pub. 17 Oct 90
302		EP #392,317 pub. 17 Oct 90

126

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
303		EP #502,314 pub. 09 Sep 92
304		EP #468,740 pub. 29 Jan 92
305		EP #470,543 pub. 12 Feb 92

TABLE II: Angiotensin II Antagonists

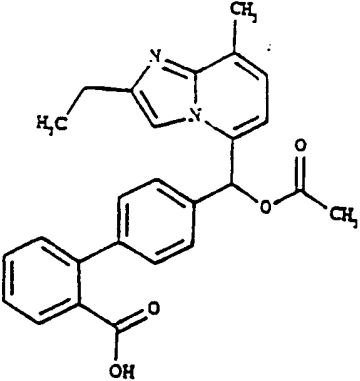
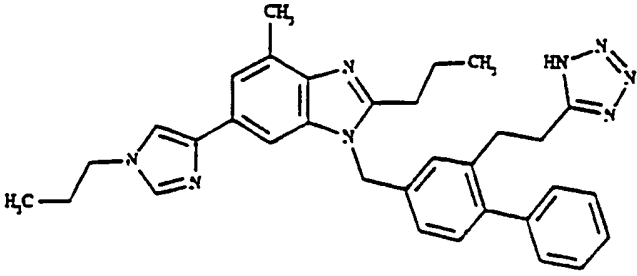
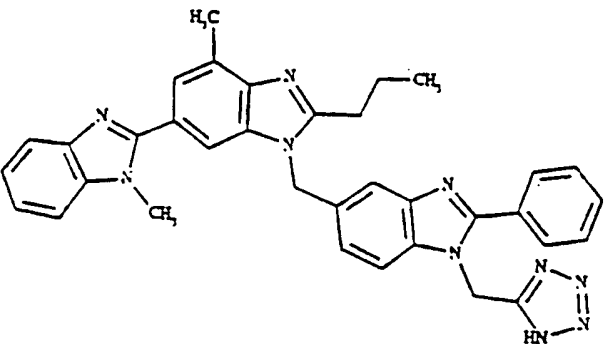
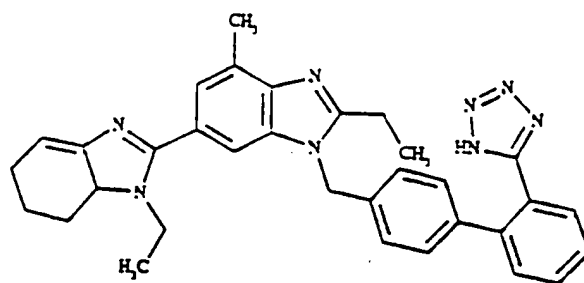
Compound #	Structure	Source
310		EP #555,825 pub. 18 Aug 93
311		EP #556,789 pub. 25 Aug 93
312		EP #560,330 pub. 15 Sep 93

TABLE II: Angiotensin II Antagonists

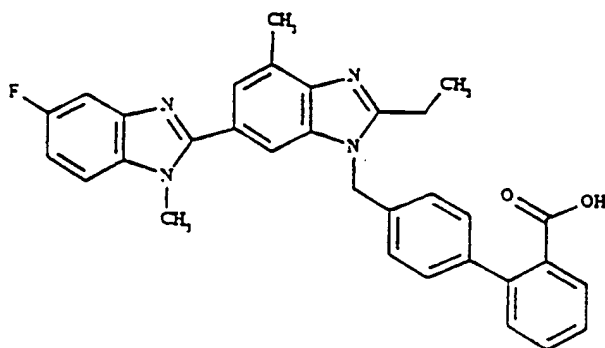
Compound #	Structure	Source
------------	-----------	--------

313



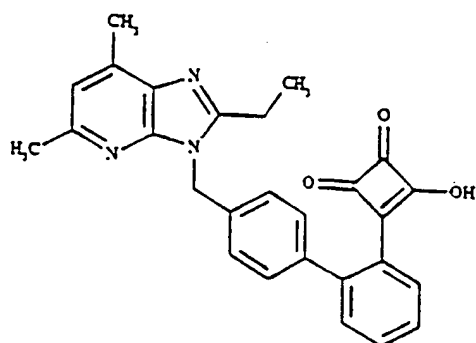
EP #566,020
pub. 20 Oct 93

314



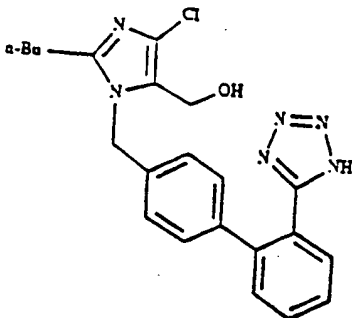
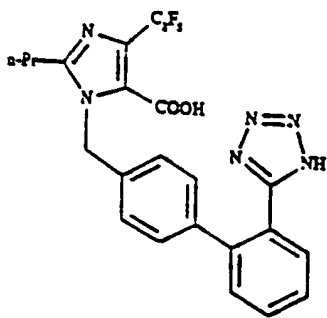
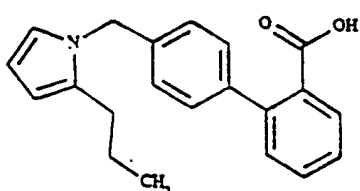
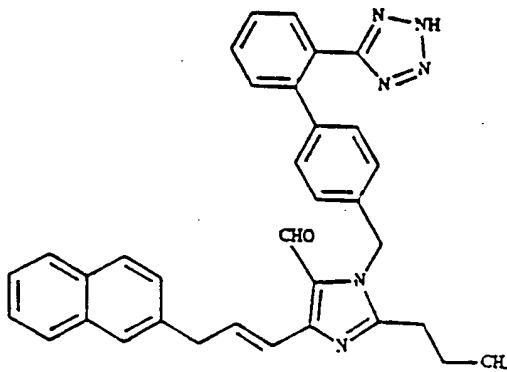
EP #581,166
pub. 02 Feb 94

315



WO #94/01436
pub. 20 Jan 94

TABLE II: Angiotensin II Antagonists

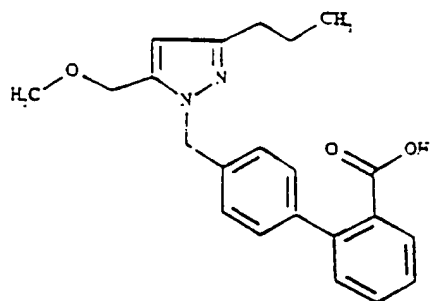
Compound #	Structure	Source
316		EP #253,310 pub. 20 Jan 88
317		EP #324,377 pub. 19 Jul 89
318		US #5,043,349 issued 27 Aug 91
319		WO #91/00281 pub. 10 Jan 91

131

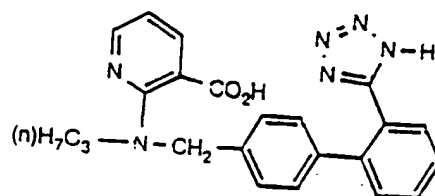
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

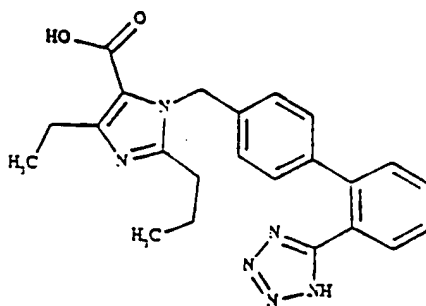
320

US #5,015,651
pub. 14 May 91

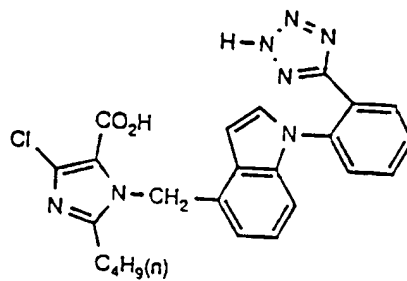
321



322

WO #92/00977
pub. 23 Jan 92

323

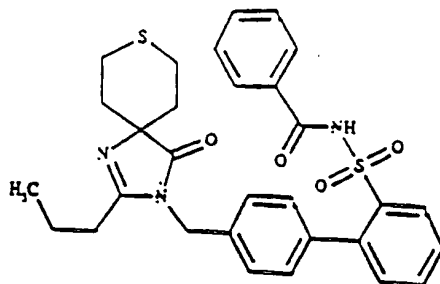


132

TABLE II: Angiotensin II Antagonists

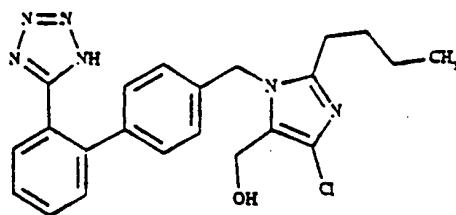
Compound #	Structure	Source
------------	-----------	--------

324



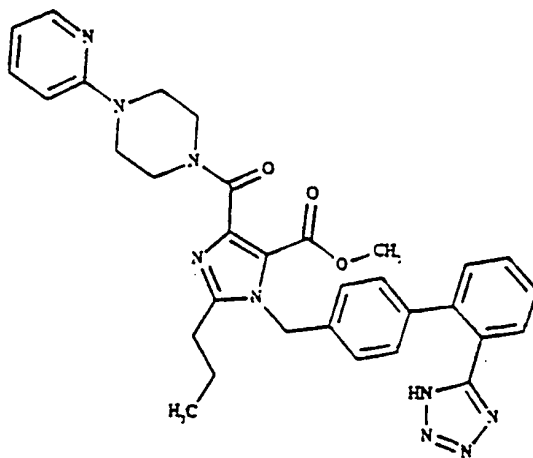
WO #93/04046
pub. 04 Mar 93

325



WO #93/10106
pub. 27 May 93

326



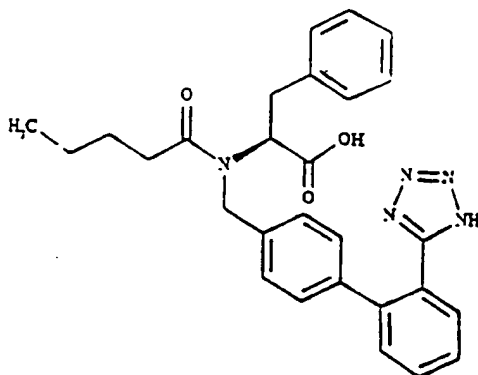
US #5,219,856
pub. 15 Jun 93

133

TABLE II: Angiotensin II Antagonists

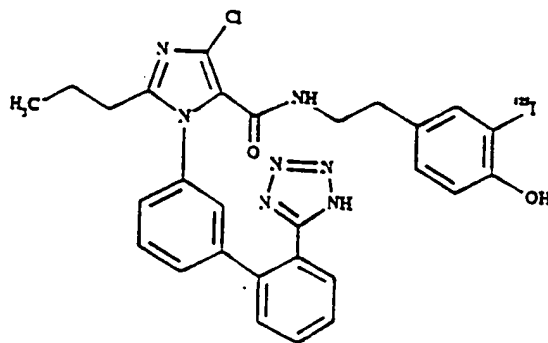
Compound #	Structure	Source
------------	-----------	--------

327



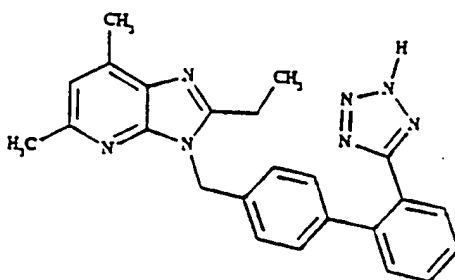
US #5,260,325
pub. 09 Nov 93

328



US #5,264,581
pub. 23 Nov 93

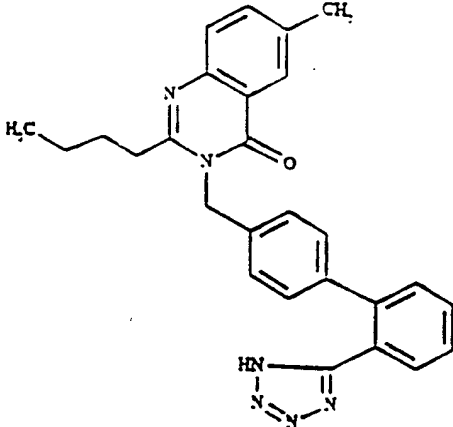
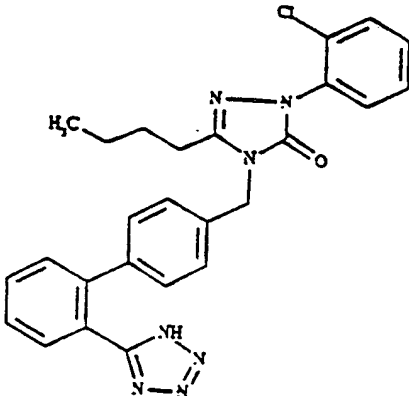
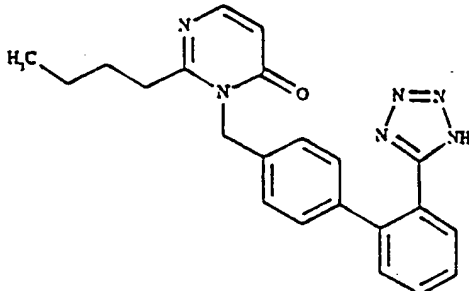
329



EP #400,974
pub. 05 Dec 90

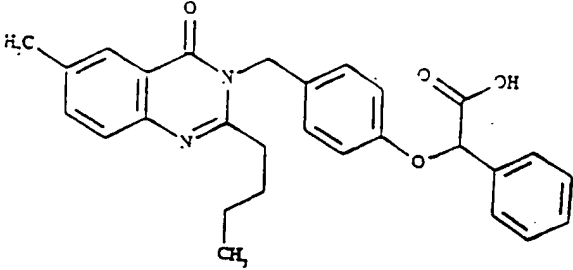
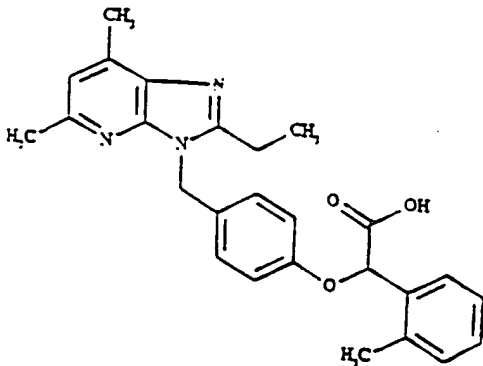
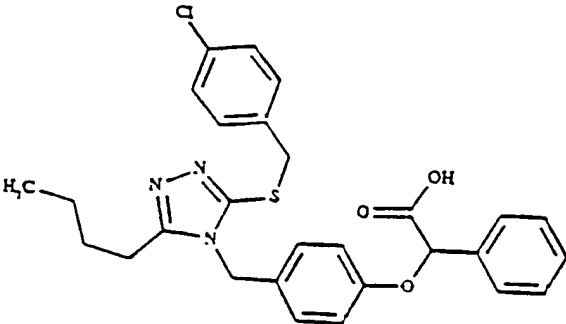
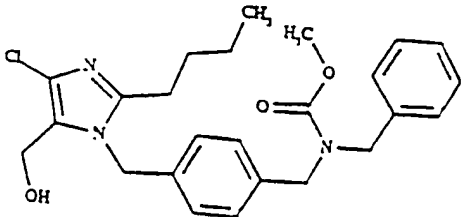
134

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
330		EP #411,766 pub. 06 Feb 91
331		EP #412,594 pub. 13 Feb 91
332		EP #419,048 pub. 27 Mar 91

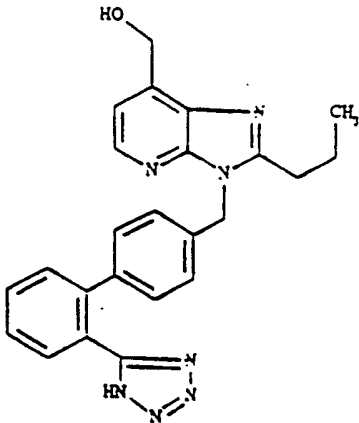
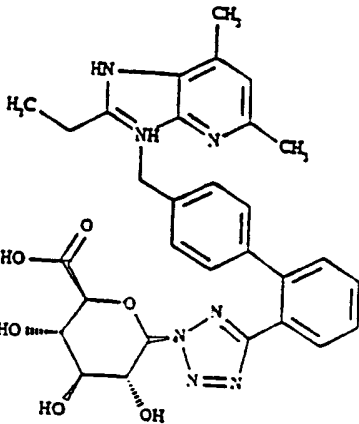
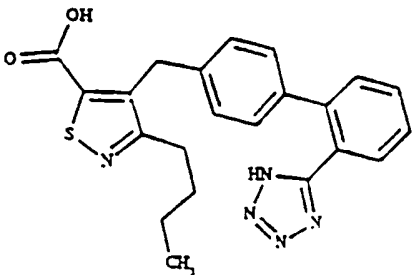
135

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
333		WO #91/12,001 pub. 22 Aug 91
334		WO #91/11,999 pub. 22 Aug 91
335		WO #91/11,909 pub. 22 Aug 91
336		WO #91/12,002 pub. 22 Aug 91

136

TABLE II: Angiotensin II Antagonists

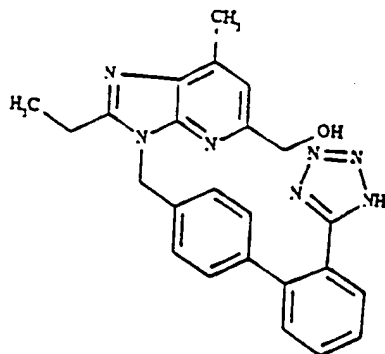
Compound #	Structure	Source
337		US #5,053,329 pub. 01 Oct 91
338		US #5,057,522 pub 15 Oct 91
339		WO #91/15,479 pub. 17 Oct 91

137

TABLE II: Angiotensin II Antagonists

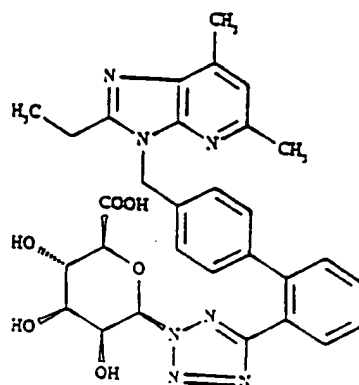
Compound #	Structure	Source
------------	-----------	--------

340



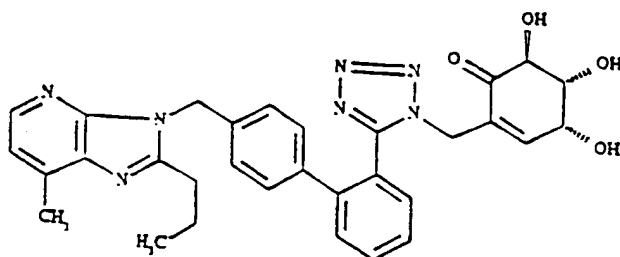
EP #456,510
pub. 13 Nov 91

341



EP #467,715
pub. 22 Jan 92

342



US #5,087,702
pub. 11 Feb 92

139

TABLE II: Angiotensin II Antagonists

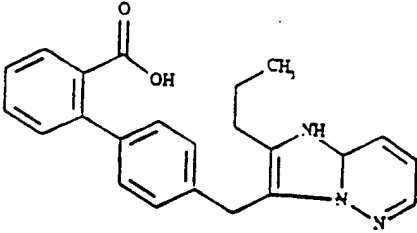
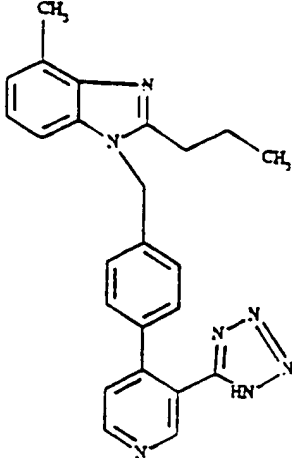
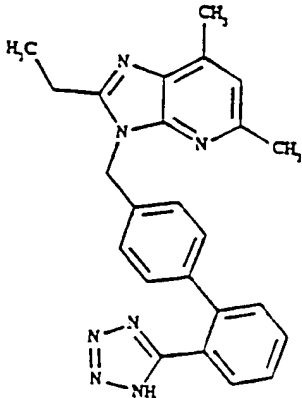
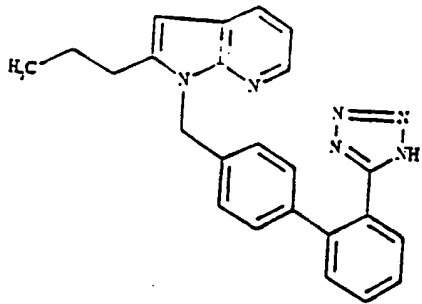
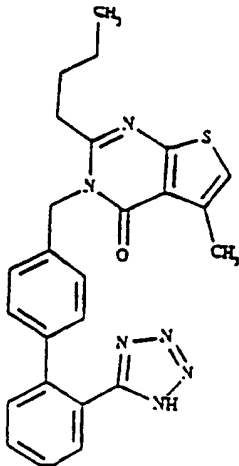
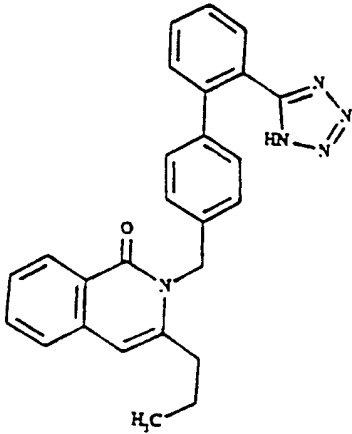
Compound #	Structure	Source
346		EP #490,587 pub. 17 Jun 92
347		US #5,128,327 pub. 07 Jul 92
348		US #5,132,216 pub. 21 Jul 92

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
349		EP #497,516 pub. 05 Aug 92
350		EP #502,725 pub. 09 Sep 92
351		EP #502,575 pub. 09 Sep 92

141

TABLE II: Angiotensin II Antagonists

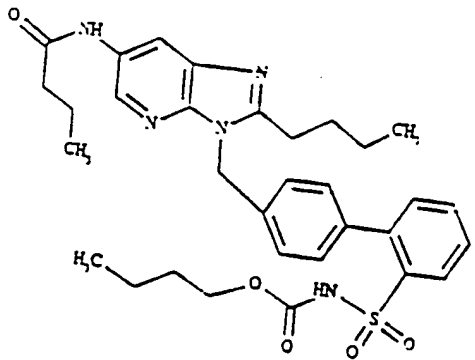
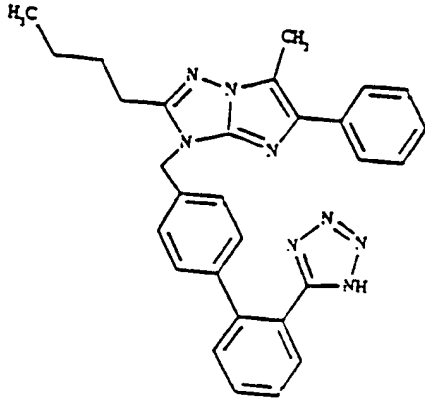
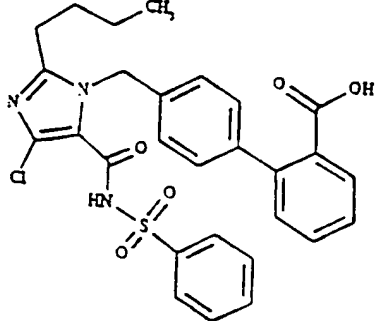
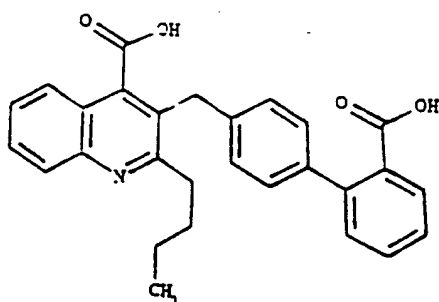
Compound #	Structure	Source
352		EP #503,838 pub. 16 Sep 92
353		EP #505,111 pub. 23 Sep 92
354		EP #505,098 pub. 23 Sep 92

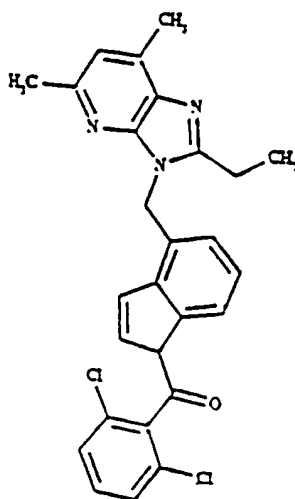
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

355

EP #507,594
pub. 07 Oct 92

356

EP #508,723
pub. 14 Oct 92

357

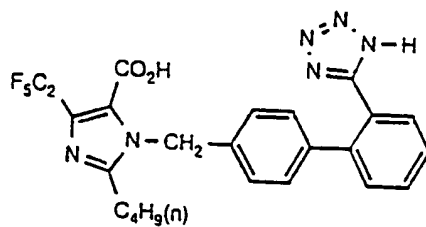


TABLE II: Angiotensin II Antagonists

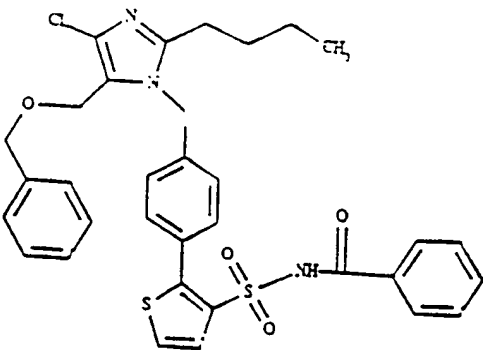
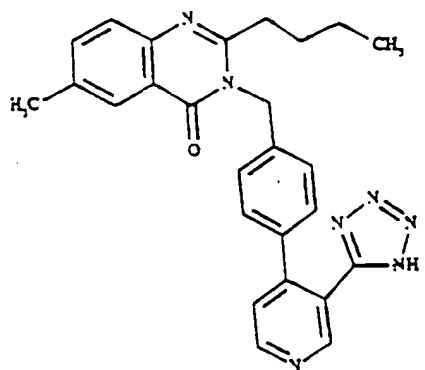
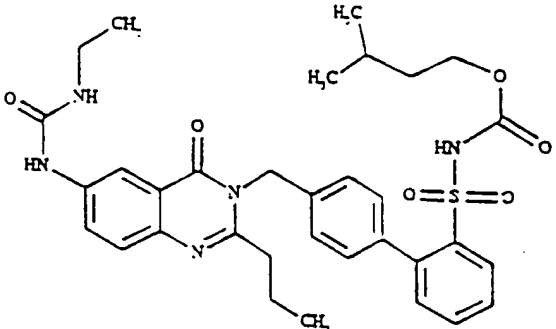
Compound #	Structure	Source
358		EP #512,675 pub. 11 Nov 92
359		EP #512,676 pub. 11 Nov 92
360		EP #512,370 pub. 11 Nov 92

TABLE II: Angiotensin II Antagonists

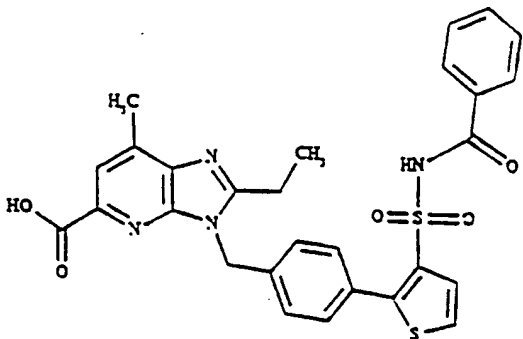
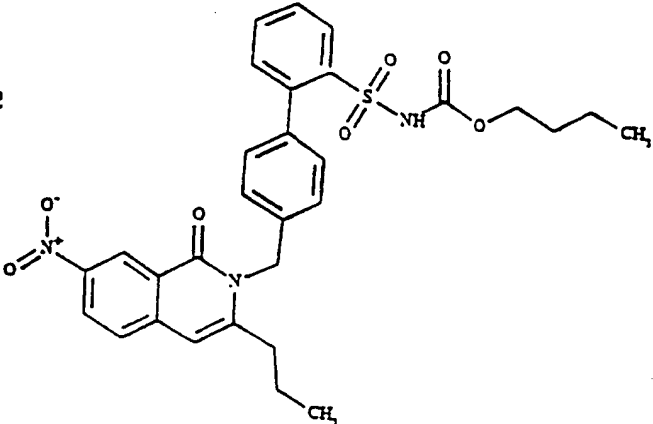
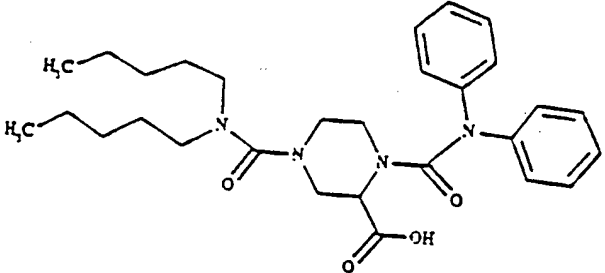
Compound #	Structure	Source
361		EP #513,979 pub. 19 Nov 92
362		WO #92/20,660 pub. 26 Nov 92
363		WO #92,20,661 pub. 26 Nov 92

TABLE II: Angiotensin II Antagonists

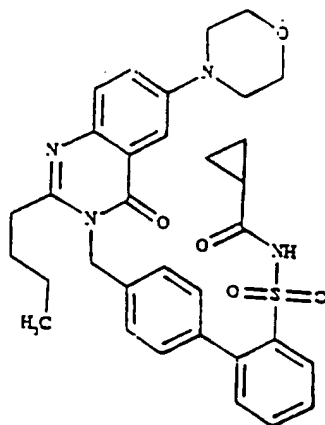
Compound #	Structure	Source
364	 <chem>CCCCN1C(=O)N(C2=CC=CC=C2C3=CC=CC=C3S(=O)(=O)NC(=O)OC(C)C)C4=CN=C(N5C(=O)C=CC=C5C6=CC=CC=C6)N1</chem>	WO #92/20,662 pub. 26 Nov 92
365	 <chem>CCCCN1C(=O)N(C2=CC=CC=C2C3=CC=CC=C3S(=O)(=O)NC(=O)OC(C)C)C4=CN=C(N5C(=O)C=CC=C5C6=CC=CC=C6)N1</chem>	WO #92/20,687 pub. 26 Nov 92
366	 <chem>CCCCN1C(=O)N(C2=CC=CC=C2C3=CC=CC=C3S(=O)(=O)NC(=O)OC(C)C)C4=CN=C(N5C(=O)C=CC=C5C6=CC=CC=C6)N1</chem>	EP #517,357 pub. 09 Dec 92

147

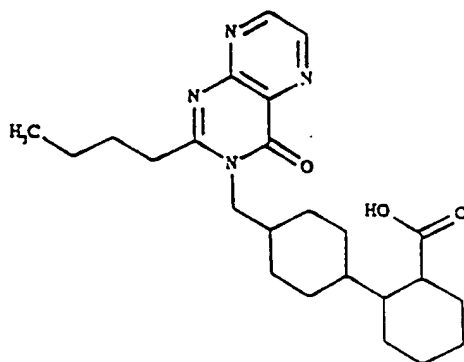
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

370

US #5,202,322
pub. 13 Apr 93

371

EP #537,937
pub. 21 Apr 93

372

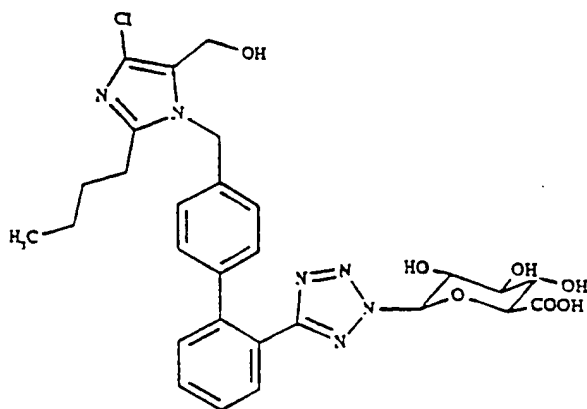
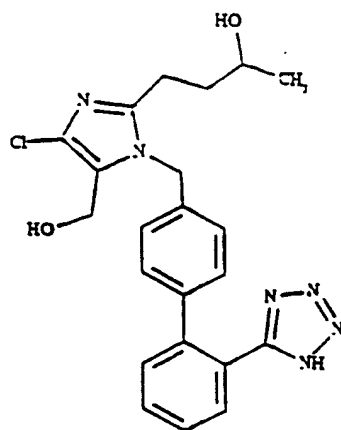
US #5,217,882
pub. 08 Jun 93

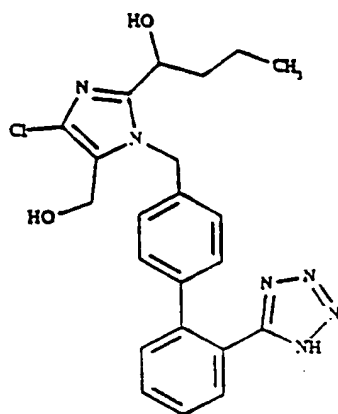
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

373

US #5,214,153
pub. 25 May 93

374

US #5,218,125
pub. 08 Jun 93

375

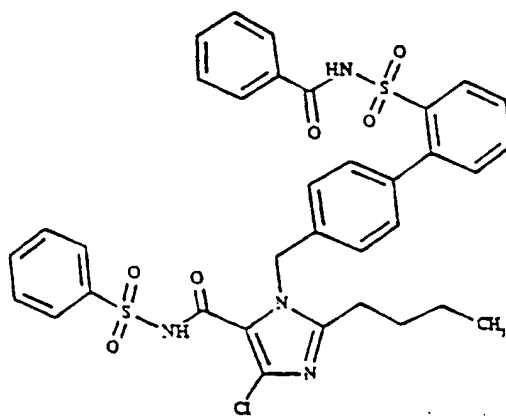
US #5,236,928
pub. 17 Aug 93

TABLE II: Angiotensin II Antagonists

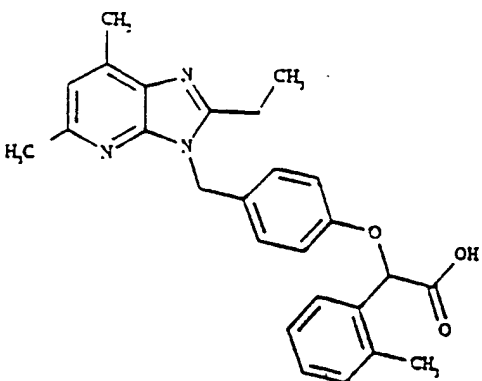
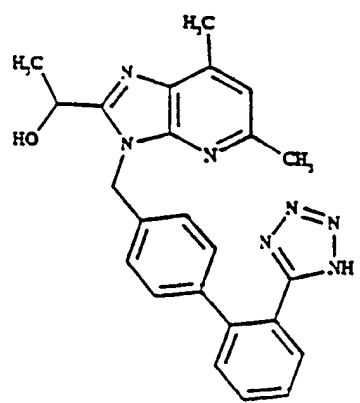
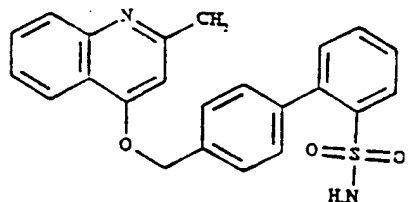
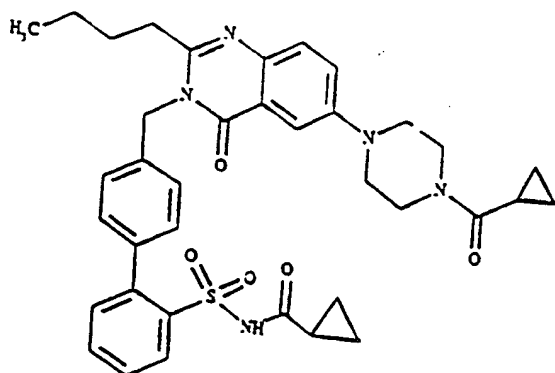
Compound #	Structure	Source
376		US #5,240,938 pub. 31 Aug 93
377		GB #2,264,709 pub. 08 Sep 93
378		GB #2,264,710 pub. 08 Sep 93

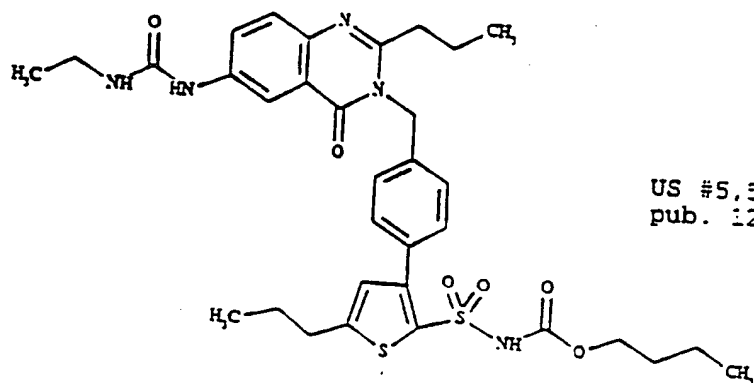
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

379

US #5,356,667
pub. 26 Oct 93

380

US #5,525,574
pub. 12 Oct 93

381

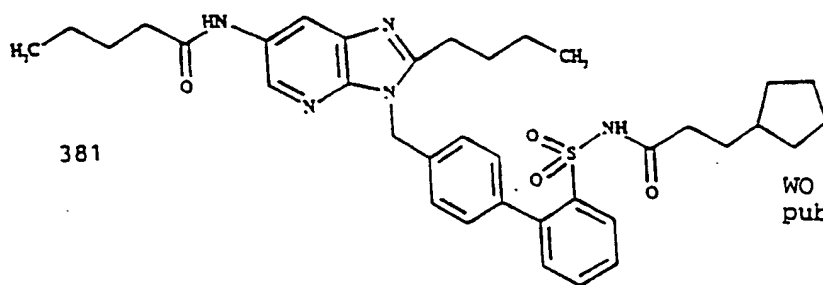
WO #93/23,399
pub. 25 Nov 93

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

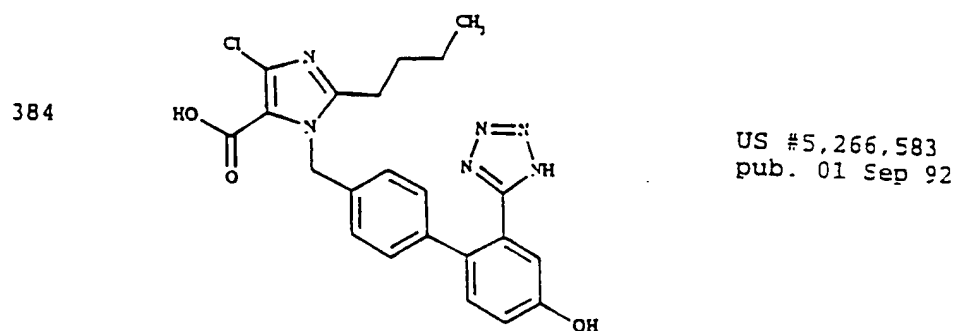
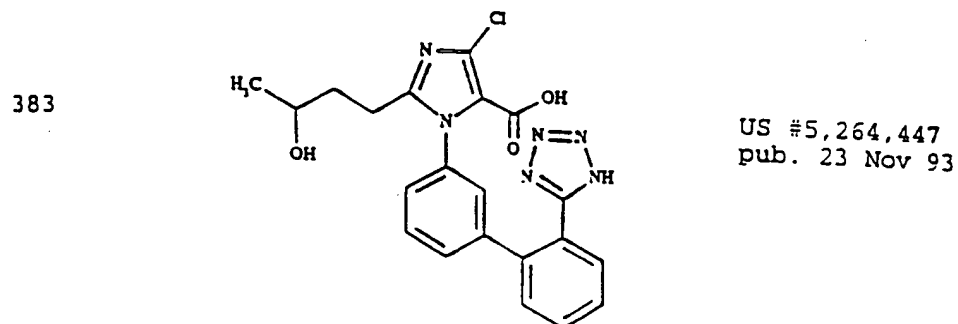
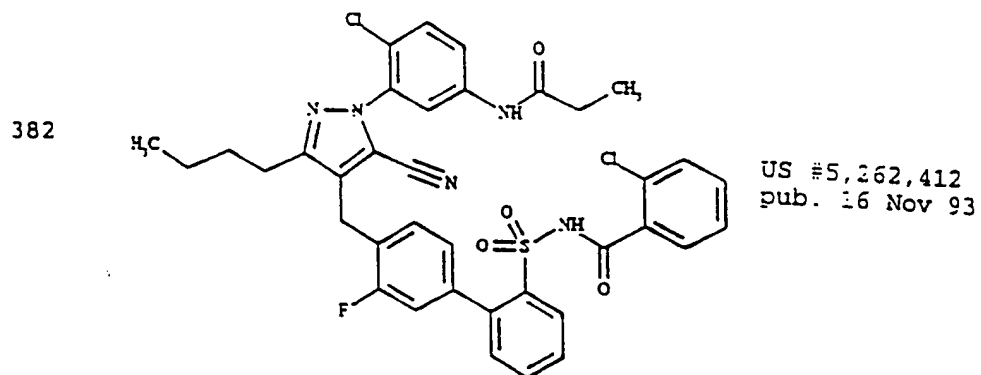
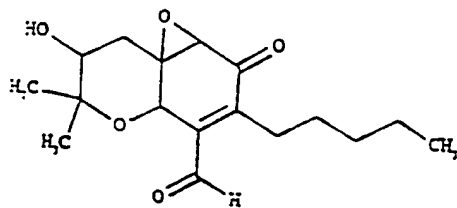
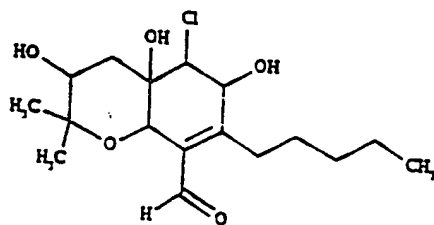


TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

385

US #5,276,054
pub. 04 Jan 94

386

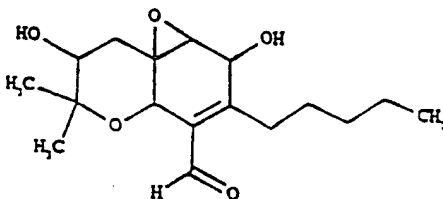
US #5,278,068
pub. 11 Jan 94

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

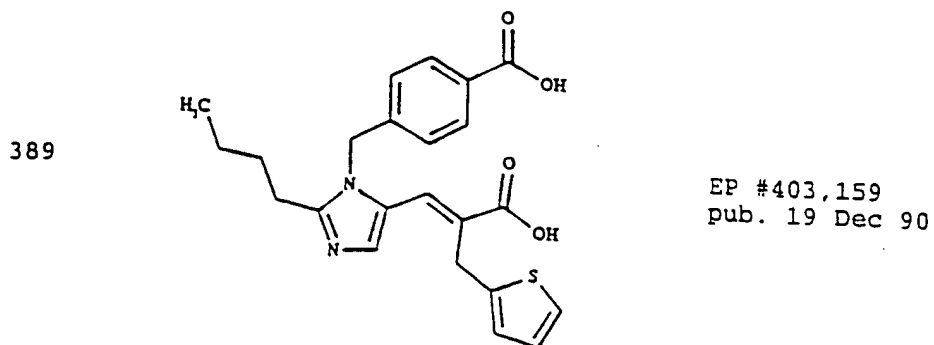
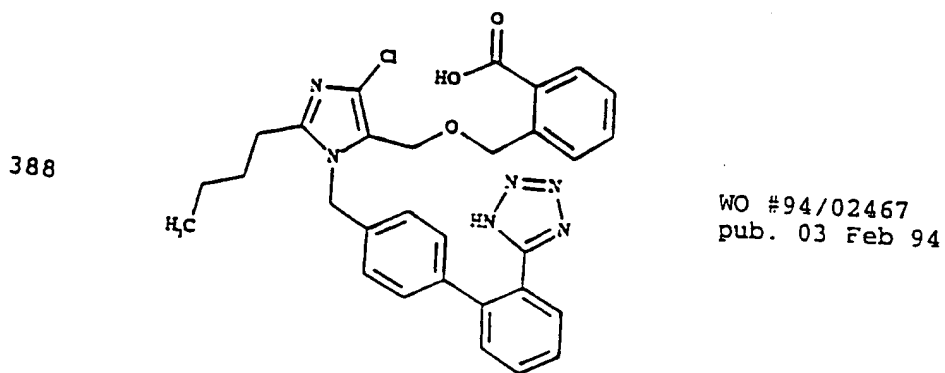
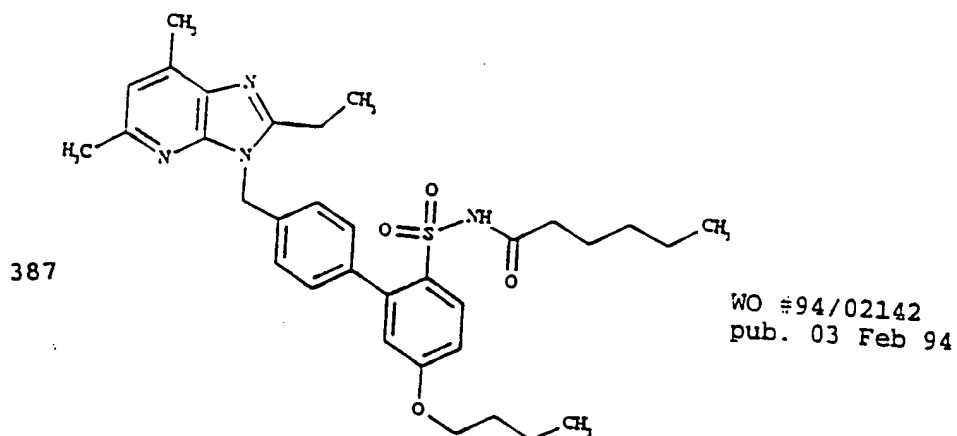


TABLE II: Angiotensin II Antagonists

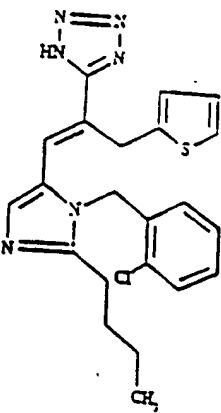
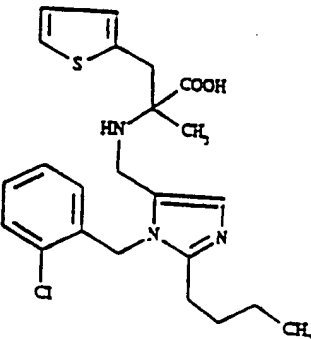
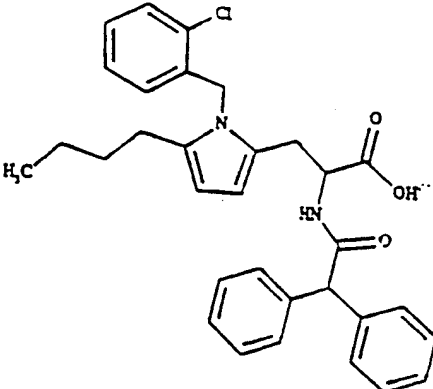
Compound #	Structure	Source
390		EP #425,211 pub. 12 May 91
391		EP #427,463 pub 15 May 91
392		WO #92/00068 pub. 09 Jan 92

TABLE II: Angiotensin II Antagonists

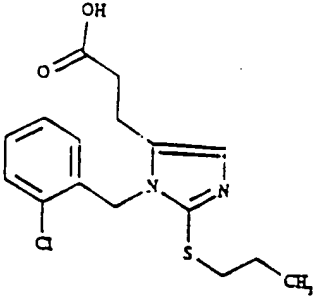
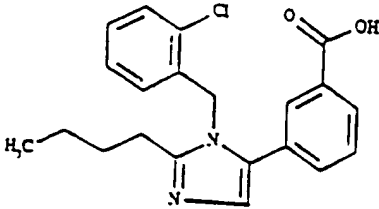
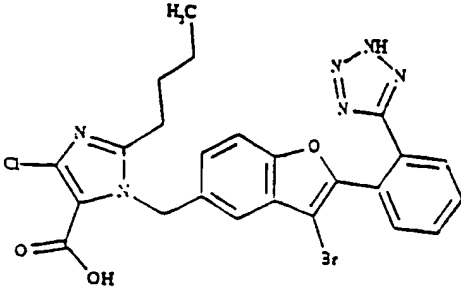
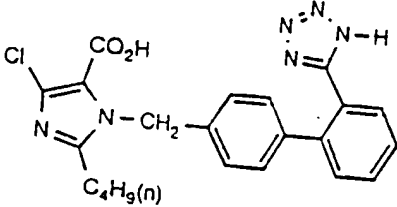
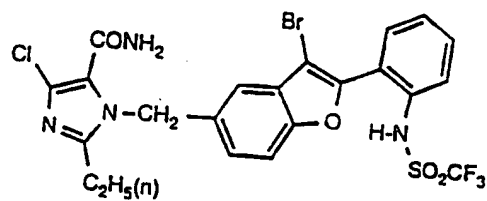
Compound #	Structure	Source
393		WO #92/02,510 pub. 20 Feb 92
394		WO #92/09278 pub. 11 Jun 92
395		WO #92/10181 pub. 25 Jun 92
396		

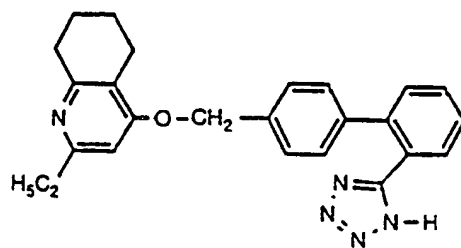
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

397



398



399

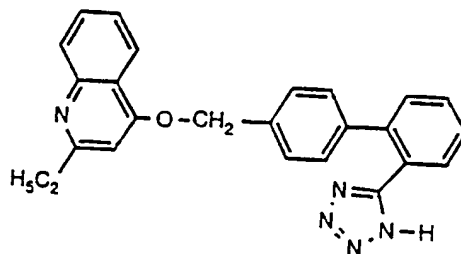
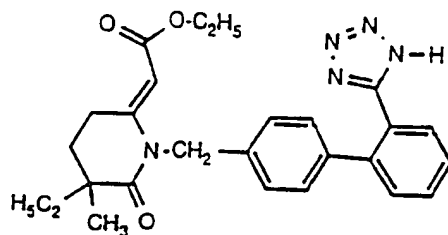


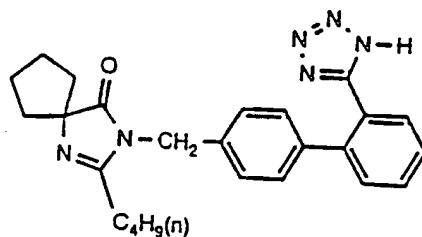
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

400



401



402

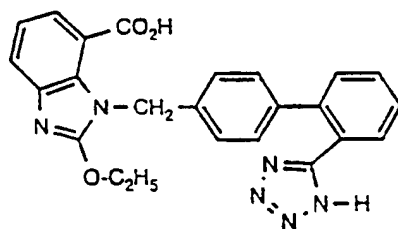
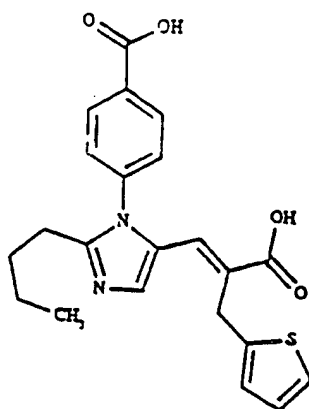


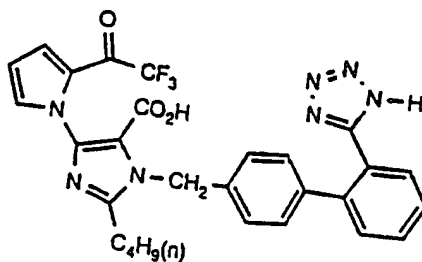
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

403

WO #92/10097
pub. 25 Jun 92

404



405

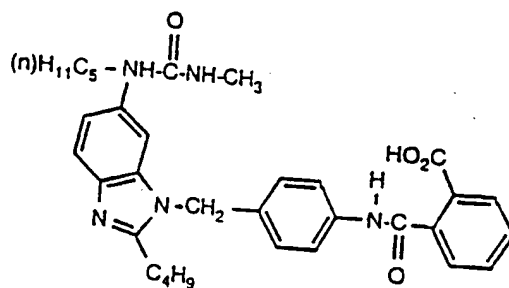
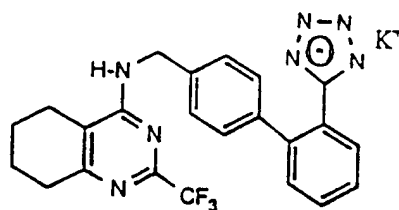


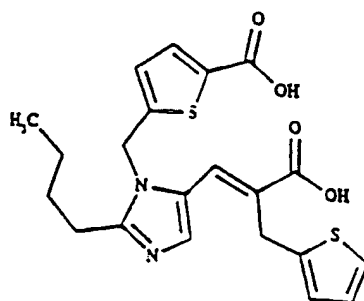
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

406



407

WO #92/20651
pub. 26 Nov 92

408

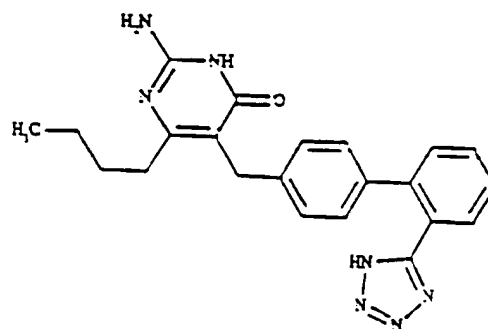
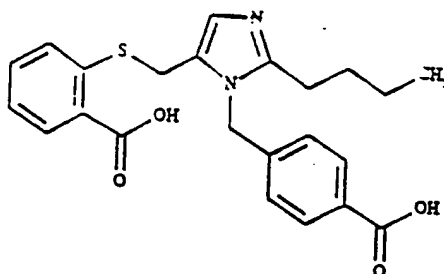
WO #93/03018
pub. 18 Feb 93

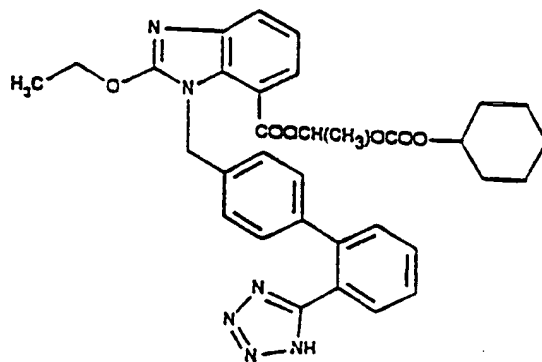
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

409

WO #94/00120
pub. 06 Jan 94

410

EP #459,136
pub. 04 Dec 91

411

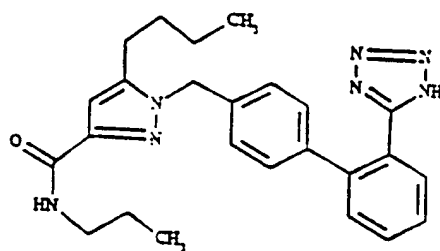
EP #411,507
pub. 05 Feb 91

TABLE II: Angiotensin II Antagonists

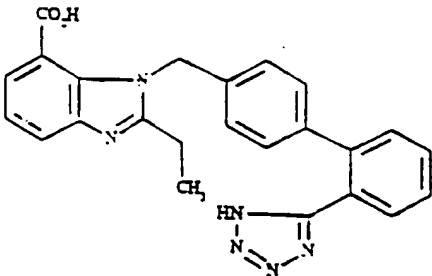
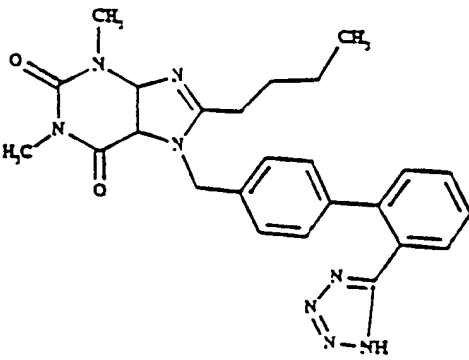
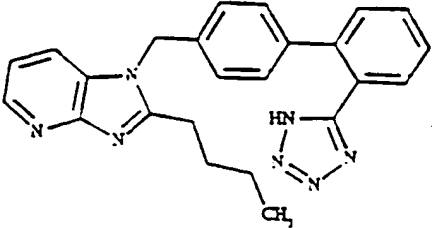
Compound #	Structure	Source
412		EP #425,921 pub. 08 May 91
413		EP #430,300 pub. 05 Jun 91
414		EP #434,038 pub. 26 Jun 91

TABLE II: Angiotensin II Antagonists

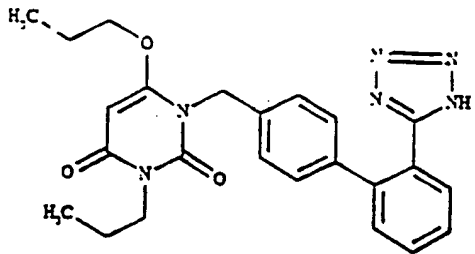
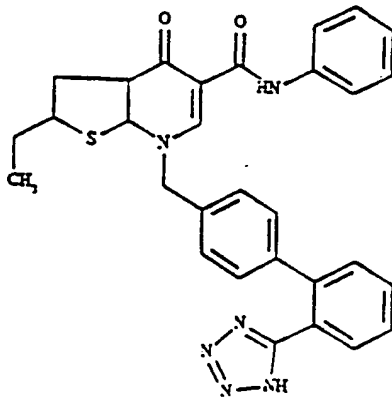
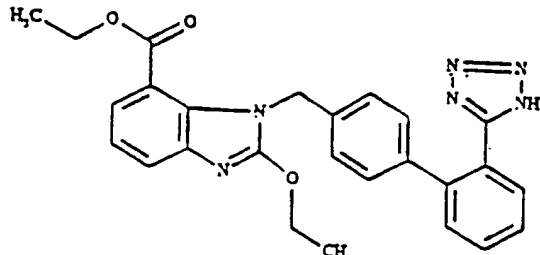
Compound #	Structure	Source
415		EP #442,473 pub. 21 Aug 91
416		EP #443,568 pub. 28 Aug 91
417		EP #459,136 pub. 04 Dec 91

TABLE II: Angiotensin II Antagonists

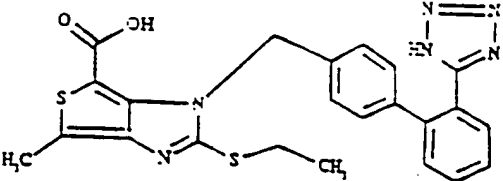
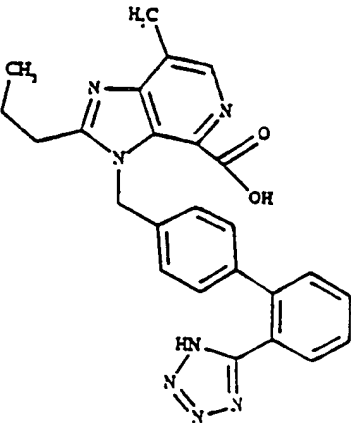
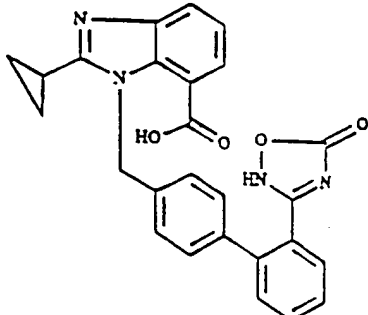
Compound #	Structure	Source
418		EP #483,683 pub. 05 May 92
419		EP #518,033 pub. 16 Dec 92
420		EP #520,423 pub. 30 Dec 92

TABLE II: Angiotensin II Antagonists

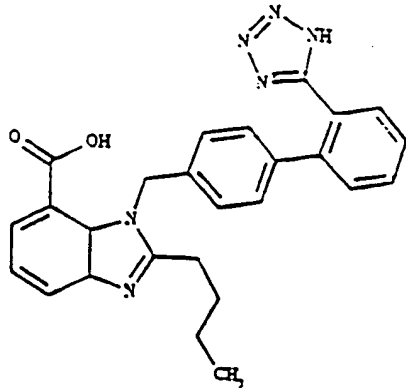
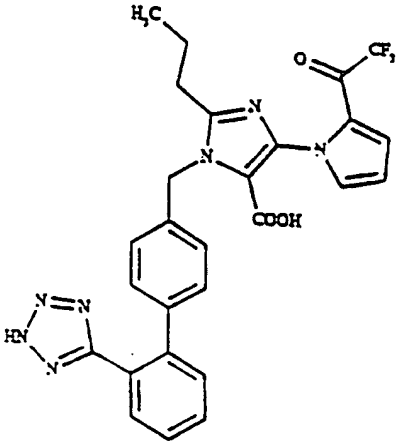
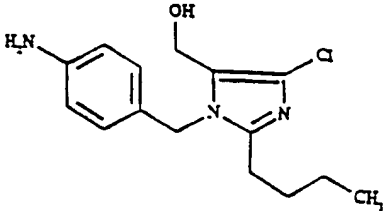
Compound #	Structure	Source
421		EP #546,358 pub. 16 Jun 93
422		WO #93/00341 pub. 07 Jan 93
423		WO #92/06081 pub. 16 Apr 92

TABLE II: Angiotensin II Antagonists

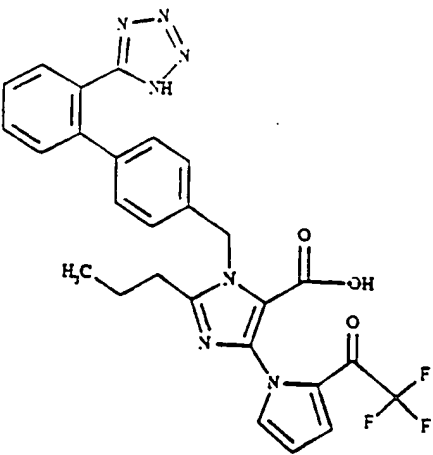
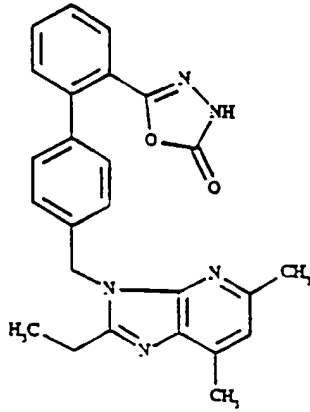
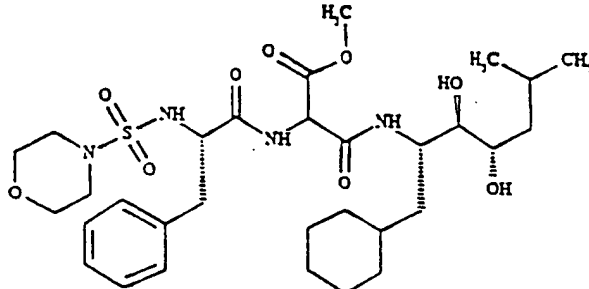
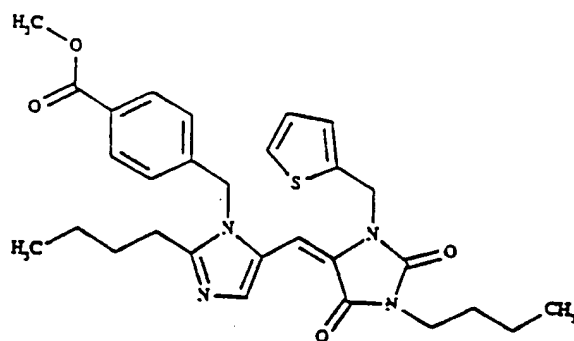
Compound #	Structure	Source
424		WO #93/00341 pub. 07 Jan 93
425		US #5,210,204 pub. 11 May 93
426		EP #343,654 pub. 29 Nov 89

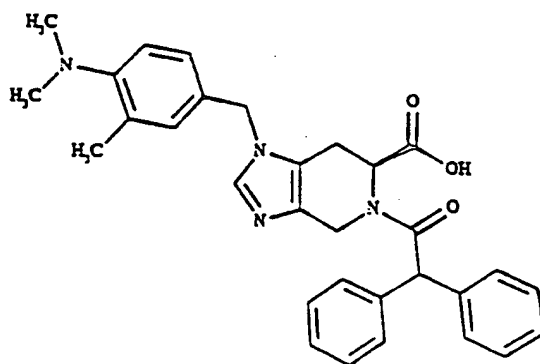
TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
------------	-----------	--------

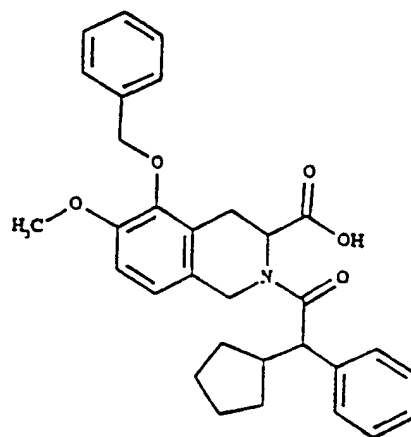
427

WO #93/13077
pub. 08 Jul 93

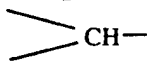
428

WO #93/15734
pub. 19 Aug 93

429

US #5,246,943
pub. 21 Sep 93

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or, as another example, one hydrido group may be attached to a carbon atom

5 to form a  group; or, as another example, two hydrido atoms may be attached to a carbon atom to form a -CH₂- group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched
10 radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The
15 term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is
20 substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a
25 fluoro atom within the group. Dihalalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two
30 chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The term "difluoroalkyl"
35 embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched

alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methylthio group. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenyl-ethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "phenalkyl" and "phenylalkyl" are interchangeable. An example of "phenalkyl" is "phenethyl" which is interchangeable with "phenylethyl". The terms "alkylaryl", "alkoxyaryl" and "haloaryl" denote, respectively, the substitution of one or more "alkyl",

"alkoxy" and "halo" groups, respectively, substituted on an "aryl" nucleus, such as a phenyl moiety. The terms "aryloxy" and "arylthio" denote radicals respectively, provided by aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes, respectively, divalent radicals SO and SO₂. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. "Lower alkanoyl" is an example of a more preferred sub-class of acyl. The term "amido" denotes a radical consisting of nitrogen atom attached to a carbonyl group, which radical may be further substituted in the manner described herein. The term "monoalkylaminocarbonyl" is interchangeable with "N-alkylamido". The term "dialkylaminocarbonyl" is interchangeable with "N,N-dialkylamido". The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted with alkyl groups which may optionally contain additional double-bond unsaturation. The term "heteroaryl", where not otherwise defined before, embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity

of the heteroaryl moiety is preserved after attachment. For any of the foregoing defined radicals, preferred radicals are those containing from one to about ten carbon atoms.

5 Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a
10 plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

 Also included in the combination of the invention
15 are the isomeric forms of the above-described angiotensin II receptor compounds and the epoxy-steroidal aldosterone receptor compounds, including diastereoisomers, regioisomers and the pharmaceutically-acceptable salts thereof. The term
 "pharmaceutically-acceptable salts" embraces salts commonly
20 used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid.
25 Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic
30 acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicylic, phenylacetic, mandelic,
35 embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic,

cyclohexylaminosulfonic, stearic, algenic, β -hydroxybutyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts include metallic salts made from aluminium, calcium, lithium, 5 magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by 10 reacting, for example, the appropriate acid or base with such compound.

BIOLOGICAL EVALUATION

In order to determine the probable effectiveness of a combination therapy for treating or preventing the progression of cardiofibrosis or cardiac hypertrophy, it is important to determine the potency of individual components of the combination therapy. Accordingly, in Assays "A" through "C", the angiotensin II receptor antagonist profiles were determined for many of the compounds described in Table II, herein. In Assay "D", there is described a method for evaluating a combination therapy of the invention, namely, an angiotensin II receptor antagonist of Table II and an epoxy-steroidal aldosterone receptor antagonist of Table I. The efficacy of each of the individual drugs, epoxymexrenone and the angiotensin II receptor blocker, and of these drugs given together at various doses, is evaluated in a rodent model. The methods and results of such assays are described below.

Assay A: Angiotensin II Binding Activity

Compounds of the invention were tested for ability to bind to the smooth muscle angiotensin II receptor using a rat uterine membrane preparation. Angiotensin II (AII) was purchased from Peninsula Labs. ^{125}I -angiotensin II (specific activity of 2200 Ci/mmol) was purchased from Du Pont-New England Nuclear. Other chemicals were obtained from Sigma Chemical Co. This assay was carried out according to the method of Douglas et al [Endocrinology, 106, 120-124 (1980)]. Rat uterine membranes were prepared from fresh tissue. All procedures were carried out at 4°C. Uteri were stripped of fat and homogenized in phosphate-buffered saline at pH 7.4 containing 5 mM EDTA. The homogenate was centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM

Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM MgCl₂, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and ¹²⁵I-AII (approximately 10⁵ cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 µM of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC₅₀) of the tested AII antagonist which gives 50% displacement of the total specifically bound ¹²⁵I-AII from the angiotensin II AT₁ receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table III.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

The compounds of the invention were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled

with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (mM): 130 NaCl, 15 NaHCO₃, 15 KCl, 1.2 NaH₂PO₄, 1.2 MgSO₄, 2.5 CaCl₂, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded (3×10^{-10} to 1×10^{-5} M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at 10^{-5} M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA₂ values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The pA₂ value is the concentration of the antagonist which increases the EC₅₀ value for AII by a factor of two. Each test antagonist was evaluated in aorta rings from two rabbits. Results are reported in Table III.

Assay C: In Vivo Intragastric Pressor Assay Response for All Antagonists

Male Sprague-Dawley rats weighing 225-300 grams were anesthetized with methohexital (30 mg/kg, i.p.) and catheters were implanted into the femoral artery and vein. The catheters were tunneled subcutaneously to exit dorsally, posterior to the head and between the scapulae. The catheters were filled with heparin (1000 units/ml of saline). The rats were returned to their cage and allowed regular rat chow and water ad libitum. After full recovery from surgery (3-4 days), rats were placed in Lucite holders and the arterial line was connected to a pressure transducer. Arterial pressure was recorded on a Gould polygraph (mmHg). Angiotensin II was administered as a 30

ng/kg bolus via the venous catheter delivered in a 50 μ l volume with a 0.2 ml saline flush. The pressor response in mm Hg was measured by the difference from pre-injection arterial pressure to the maximum pressure achieved. The AII injection was repeated every 10 minutes until three consecutive injections yielded responses within 4 mmHg of each other. These three responses were then averaged and represented the control response to AII. The test compound was suspended in 0.5% methylcellulose in water and was administered by gavage. The volume administered was 2 ml/kg body weight. The standard dose was 3 mg/kg. Angiotensin II bolus injections were given at 30, 45, 60, 75, 120, 150, and 180 minutes after gavage. The pressor response to AII was measured at each time point. The rats were then returned to their cage for future testing. A minimum of 3 days was allowed between tests. Percent inhibition was calculated for each time point following gavage by the following formula: [(Control Response - Response at time point)/Control Response] X 100. Results are shown in Table III.

Assay "D": Renal Hypertensive Rat Model

A combination therapy of an angiotensin II receptor antagonist and an epoxy-steroidal aldosterone receptor antagonist may be evaluated for blood pressure lowering activity in the renal-artery ligated hypertensive rat, a model of high renin hypertension. In this model, six days after ligation of the left renal artery, both plasma renin activity and blood pressure are elevated significantly [J.L. Cangiano et al, J. Pharmacol. Exp. Ther., 206, 310-313 (1979)]. Male Sprague-Dawley rats are instrumented with a radiotelemetry blood pressure transmitter for continuous monitoring of blood pressure. The rats are anesthetized with a mixture of ketamine-HCl (100 mg/kg) and acepromazine maleate (2.2 mg/kg). The abdominal aorta is exposed via a midline incision. Microvascular clamps are placed on the

aorta distal to the renal arteries and at the iliac bifurcation. The aorta is punctured with a 22-gauge needle and the tip of a catheter is introduced. The catheter, which is held in place by a ligature in the psoas muscle, is connected to a radiotelemetry blood pressure transmitter (Mini-Mitter Co., Inc., Sunriver, OR). The transmitter is placed in the peritoneal cavity and sutured to abdominal muscle upon closing of the incision. Rats are housed singly above a radiotelemetry receiver and are allowed standard rat chow and water *ad libitum*. At least 5 days are allowed for recovery from surgery. Mean arterial pressure and heart rate are measured on a Compaq DeskPro 286 AT computer. Data are sampled for 10 seconds at 200-500 hz at 2.5 to 10 min intervals 24 hours per day. After collecting control data for 24 hours, the rats are anesthetized with methohexital (30 mg/kg, i.p.) and supplemented as needed. A midline abdominal incision is made, approximately 2cm in length to expose the left kidney. The renal artery is separated from the vein near the aorta, with care taken not to traumatize the vein. The artery is completely ligated with sterile 4-0 silk. The incision is closed by careful suturing of the muscle layer and skin. Six days later, when MAP is typically elevated by 50-70 mmHg, an AII receptor antagonist, or an aldosterone receptor antagonist, or a combination of the two compounds are administered by gavage each day for about 8 weeks. Single drug dosing is carried out using 20 and 200 mg/kg/day of epoxymexrenone and 1,3,10,30 and 100 mg/kg/day of an AII receptor antagonist. Drug mixtures are obtained by administering a combination of a dose of 1,3,10,30 or 100 mg/kg/day of the AII receptor antagonist with a dose of either 20 or 200 mg/kg/day of the aldosterone antagonist. Blood pressure lowering is monitored by the radiotelemetry system and responses with the compounds are compared to responses obtained in vehicle-treated animals. Plasma and urinary sodium and potassium levels are monitored as a measure of the effectiveness of the aldosterone blockade. Urine samples are collected

overnight using metabolic cages to isolate the samples.
Plasma samples are obtained by venous catheterization.
Sodium and potassium are measured by flame photometry.
Cardiac fibrosis is determined by histological and chemical
5 measurements of the excised hearts following perfusion
fixation. Left and right ventricles are weighed, embedded
and sectioned. Subsequently, sections are stained with
picrosirius red and the red staining collagen areas are
quantitated by computerized image analysis. The apex of the
10 heart is acid digested and the free hydroxyproline measured
colorimetrically. It is expected that MAP will be
significantly lowered toward normal pressures in the test
animals, treated with the combination therapy and that the
condition of myocardial fibrosis will be arrested or
15 avoided.

TABLE III

In Vivo and In Vitro Angiotensin II
Activity of Compounds of the Invention

Test Compound Example #	¹ Assay A	² Assay B	³ Assay C		
	IC ₅₀	pA ₂	Dose	Inhibition	Duration
	(nM)		(mg/kg)	(%)	(min.)
1	NT	NT	NT	NT	NT
10	2	95	7.37/7.59	10	95
			30	98	90-120
	3	5.4	8.70 ± 0.2	10	50
			30	100	200+
4	NT	NT	NT	NT	NT
15	5	200	7.48/6.91	30	38
	6	1300	6.55/6.82	100	90
	7	84	8.01/8.05	30	90
	8	17,000	NT	NT	NT
20	9	700	6.67/6.12	30	80
			100	100	130
	10	4.9	8.19/7.59	3	86
			30	100	240
	11	160	6.45/6.77	NT	NT
	12	6.0	8.66/8.59	NT	NT
25	13	17	8.70/8.85	NT	NT
	14	7.2	8.84/8.71	NT	NT
	15	16	8.31/8.30	NT	NT
	16	6.4	8.95/9.24	NT	NT
	17	4.0	8.64/8.40	NT	NT
30	18	970	6.14/6.09	NT	NT
	19	12,000	5.18/5.35	NT	NT

Test	Compound	¹ Assay A	² Assay B	³ Assay C		
		IC ₅₀	pA ₂	Dose	Inhibition	Duration
		(nM)		(mg/kg)	(%)	(min.)
5	20	78,000	5.89/5.99	100	10	45
	21	87	7.71/7.21	NT	NT	NT
	22	460	6.60/6.46	NT	NT	NT
	23	430	6.48/7.15	NT	NT	NT
	24	10	7.56/7.73	NT	NT	NT
10	25	480	6.80/6.73	NT	NT	NT
	26	3.2	9.83/9.66	10	50	>180
	27	180	NT	NT	NT	NT
	28	570	5.57/6.00	NT	NT	NT
	29	160	NT	NT	NT	NT
15	30	22	7.73/7.88	30	50	>180
	31	14	NT	NT	NT	NT
	32	16	7.68/7.29	NT	NT	NT
	33	630	6.73/6.36	NT	NT	NT
	34	640	5.34/5.69	NT	NT	NT
20	35	41	7.25/7.47	NT	NT	NT
	36	1400	5.92/5.68	NT	NT	NT
	37	340	6.90/6.85	NT	NT	NT
	38	10	7.82/8.36	NT	NT	NT
	39	10	7.88/7.84	NT	NT	NT
25	40	83	7.94/7.61	NT	NT	NT
	41	3700	5.68/5.96	NT	NT	NT
	42	370	6.56/6.26	NT	NT	NT
	43	19	8.97/8.61	NT	NT	NT
	44	16	8.23/7.70	NT	NT	NT
30	45	4.4	8.41/8.24	NT	NT	NT
	46	110	6.80/6.64	NT	NT	NT

Test Compound	Example #	¹ Assay A	² Assay B	³ Assay C		
		IC ₅₀ (nM)	pA ₂	Dose (mg/kg)	Inhibition (%)	Duration (min.)
5	47	21	7.85/7.58	NT	NT	NT
	48	680	6.27/6.75	NT	NT	NT
	49	120	7.06/7.07	NT	NT	NT
	50	54	7.71/7.89	NT	NT	NT
	51	8.7	8.39/8.51	NT	NT	NT
10	52	100	8.14/8.12	NT	NT	NT
	53	65	7.56/7.83	NT	NT	NT
	54	3100	6.02	NT	NT	NT
	55	80	6.56/7.13	NT	NT	NT
	56	5.0	9.04/8.35	NT	NT	NT
15	57	2300	6.00	NT	NT	NT
	58	140	6.45/6.57	NT	NT	NT
	59	120	7.23/7.59	NT	NT	NT
	60	2200	6.40/6.03	NT	NT	NT
	61	110	7.29/7.70	NT	NT	NT
20	62	26	8.69/8.61	NT	NT	NT
	63	61	7.77/7.67	NT	NT	NT
	64	54	7.00/6.77	NT	NT	NT
	65	23	7.85/7.75	NT	NT	NT
	66	12	9.34/8.58	NT	NT	NT
25	67	3100	5.88/5.78	NT	NT	NT
	68	8.6	8.19/8.65	NT	NT	NT
	69	15	7.80/8.28	NT	NT	NT
	70	44	7.71/8.05	NT	NT	NT
	71	12,000	*	NT	NT	NT
30	72	83	6.11/6.10	NT	NT	NT
	73	790	7.65/7.46	NT	NT	NT

Test	¹ Assay A		² Assay B		³ Assay C	
	Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
5	74	6.5	8.56/8.39	NT	NT	NT
	75	570	6.00/5.45	NT	NT	NT
	76	5400	5.52/5.78	NT	NT	NT
	77	15,000	5.77	NT	NT	NT
	78	101	7.0		93	60-100
10	79	4.9	9.2		100	>200
					50	>180
	80	25	8.1		NT	NT
	81	18	8.0		40	180
	82	7.9	8.5		20	180
15	83	3.6	8.3		15	>180
	84	16	7.1		20	30
	85	8.7	8.9		NT	NT
	86	9	7.8		NT	NT
	87	91	7.8		NT	NT
20	88	50	7.7		NT	NT
	89	18	7.9		NT	NT
	90	5.6	9.0		NT	NT
	91	30	8.6		40	>180
	92	35	7.9		NT	NT
25	93	480	NT		NT	NT
	94	5,800	NT		NT	NT
	95	66	8.2		NT	NT
	96	21	8.0		NT	NT
	97	280	7.7		NT	NT
30	98	22	8.1		NT	NT
	99	280	6.5		NT	NT
	100	4.4	9.4		NT	NT
	101	36	7.8		NT	NT

Test	Compound	¹ Assay A	² Assay B	³ Assay C		
		IC ₅₀	pA ₂	Dose	Inhibition	Duration
Example #		(nM)		(mg/kg)	(%)	(min.)
5	102	43	7.7		NT	NT
	103	12	8.0		NT	NT
	104	15	8.0		NT	NT
	105	290	6.6		NT	NT
	106	48	7.7		NT	NT
10	107	180	8.3		NT	NT
	108	720	5.3	100	45	90
	109	250	7.3	30	50	30
	110	590	6.4		NT	NT
	111	45	9.0	30	87	160
15	112	2000	5.2		NT	NT
	113	12	8.4	10	60	180
	114	400	6.4		NT	
	115	11	8.2	3	40	>240
	116	230	6.5		NT	
20	117	170	6.5		NT	
	118	37	9.21/9.17	10	70	120
	119	16	9.21/9.00	3	20	60
	120	25	9.05/8.77	10	80	240
	121	46	NT		NT	
25	122	46	NT		NT	
	123	50	NT		NT	
	124	40	9.42/9.12	3	45	>180
	125	40	9.25/8.80	3	35	>240

Test	¹ Assay A		² Assay B		³ Assay C	
	Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
5	126	240	7.20/7.05		NT	
	127	12,000	4.96		NT	
	128	16	8.63/8.40		NT	
	129	6,700	5.30		NT	
	130	40	8.10/7.94		NT	
10	131	9.5	7.53/8.25			
	132	12	8.6		NT	
	133	10	8.7	3	20	180
						90-120
	134	22	9.3	3	35	180
15	135	16	8.5	3	35	>180
	136	NT	NT		NT	
	137	220	8.3		NT	
	138	130	8.2		NT	
	139	0.270	6.3		NT	
20	140	0.031	8.1		100	160
	141	0.110	8.02		NT	NT
	142	2.000	NA		NT	NT
	143	0.052	7.7		85	75
	144	0.088	7.7		50	125
25	145	0.480	6.7		NT	NT
	146	0.072	6.4		NT	NT

Test	¹ Assay A	² Assay B	³ Assay C			
Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration	
Example #	(nM)		(mg/kg)	(%)	(min.)	
5	147	5.8	5.6	3	74	5-10
	148	0.87	5.8	3	92	20-30
	149	1.1	6.1	3	NT	NT
	150	14	8.03/7.80	3	25	>180
	151	17	7.76/7.97	3	15	180
10	152	150	7.46/7.23	3	10	140
	153	13	8.30/7.69	3	25	>180
	154	97	8.19/8.38		NA	
	155	86	7.60/7.14		NA	
	156	78	8.03/7.66		NA	
15	157	530	- /6.22		NA	
	158	54	8.23/8.14	3	30	>180
	159	21	7.92/7.56	3	10	150
	160	64	7.87/7.71			
	161	28			NA	
20	162	380	6.21/6.55		NA	
	163	420	7.42/6.75		NA	
	164	1700			NA	
	165	410	6.90/7.18		NA	

Test Compound	¹ Assay A	² Assay B	³ Assay C		
	IC ₅₀	pA ₂	Dose	Inhibition	Duration
Example #	(nM)		(mg/kg)	(%)	(min.)
5	166	160	7.57/7.74		NA
	167	370	7.08/7.11		NA
	168	420	7.69/7.58		NA
	169	150	7.78/7.58	3	15
	170	26	7.08/7.77	3	40
10	171	28	7.52/7.11	3	0
	172	70	7.15/7.04		NA
	173	90	7.49/6.92		NA
	174	180	7.29/7.02		NA
	175	27	NA	3	0
15	176	9.8	7.69/7.55	3	10
	177	26	7.41/7.85	3	15
	178	88	7.54/7.47		NA
	179	310	6.67/ -		NA
	180	20	7.56/7.15	3	25
20	181	21	7.70/7.12	3	20
	182	59	NA		NA
	183	390	NA		NA
	184	1100	6.78/ -		NA

186

Test	Compound	¹ Assay A	² Assay B	³ Assay C		
		IC ₅₀	pA ₂	Dose	Inhibition	Duration
Example #		(nM)		(mg/kg)	(%)	(min.)
5	185	6.5	8.82/8.53	3	50	> 180
	186	38	8.13/7.40	3	25	180
	187	770	7.46/6.95		NA	
	188	140	7.72/7.09		NA	
	189	29	8.64/8.23		NA	
10	190	10	7.87/7.89	3	10	180
	191	81	7.75/7.76	3	10	180
	192	140			NA	
	193	11	9.27/8.87	3	10	180
	194	47	7.64/7.35		NA	
15	195	34	8.44/8.03		NA	
	196	31	7.68/8.26		NA	
	197	14	8.03/8.60		NA	
	198	7.6	8.76/8.64	3	35	> 180
	199	10	8.79/8.85	3	60	> 180
20	200	20	8.42/8.77	3	45	> 180
	201	17	8.78/8.63	3	10	180
	202	12	8.79/8.64	3	65	> 180
	203	9.2	8.43/8.36	3	50	> 180
	204	16	9.17/8.86	3	75	> 180
25	205	20	9.14/9.15	3	40	> 180
	206	5.4	8.75/8.89	3	30	> 180
	207	99	9.04/8.60		NA	
	208	22	9.19/8.69	3	50	> 180
	209	5.0	9.41/9.16	3	25	> 180
30	210	3.6	8.36/8.44	3	15	180
	211	18	8.74/8.67	3	35	> 180
	212	23	8.85/8.25	3	15	180
	213	51	NA		NA	
	214	65	NA		NA	
35	215	45	NA		NA	
	216	5.4	8.80/9.04	3	50	> 180

Test	¹ Assay A	² Assay B	³ Assay C			
Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration	
Example #	(nM)		(mg/kg)	(%)	(min.)	
5	217	9.4	NA	3	65	> 180
	218	9.0	NA		NA	
	219	14	NA		NA	
	220	7.0	NA	3	75	120
10	221	4.8	NA	3	25	> 180
	222	5.0	NA		NA	
	223	14	7.45/7.87	3	20	> 180
	224	91	NA		NA	
	225	160	NA		NA	
15	226	93	NA		NA	
	227	89	7.55/7.67		NA	
	228	4.5	9.17/8.25	3	80	>180
	229	19	NT	3	40	>180
	230	2.6	8.23/8.69	3	25	>180
20	231	3.6	NT	3	75	>180
	232	4.4	8.59/8.89	3	70	>180
	233	84	8.51/8.78		NT	
	234	5.0	8.49/9.00	3	20	-
	235	34	7.14/7.07		NT	
25	236	4.9	NC	3	70	>180
	237	3.6	NT		NT	
	238	1.7	NT	3	15	>180
	239	6.8	7.88/8.01	3	20	>180
	240	120	NA		NA	
30	241	6.9	8.57/8.24	3	40	>180
	242	110	7.11/6.60		NA	
	243	250	NA		NA	
	244	150	7.17/7.17		NA	
	245	98	6.64/7.04		NA	
35	246	72	7.46/7.59		NA	
	247	9.4	8.26/8.41	3	20	180

Test	¹ Assay A	² Assay B	³ Assay C		
Compound	IC ₅₀	pA ₂	Dose	Inhibition	Duration
Example #	(nM)		(mg/kg)	(%)	(min.)
5	248	20	7.68/7.50	3	10
	249	4.4	NA	3	20
	250	43	NA	3	0
	251	25	NA		NA
	252	13	NA		NA
10	253	2.6	NA		NA
	254	72	NA		NA
	255	12	7.61/7.46	3	20
	256	4.1	8.43/7.78	3	30
	257	160	6.63/6.68		NA
15	258	350	6.84/6.84		NA
	259	54	NA		NA
	260	220	NA		NA
	261	18	NA		NA
	262	530	-/6.22		NA
20	263	57	NA		NA
	264	11	NA		NA
	265	110	NA		NA
	266	290	NA		NA
	267	25	NA	3	25
25	268	520	NA	3	0
	269	9.7	NA		NA
	270	21	NA		NA
	271	14	NC	3	20%
	272	97	NC	3	70%
30	273	9.8	8.53/8.61	3	25%
	274	13	9.06/8.85	3	35%
	275	6.3	9.07/ --	3	40%
	276	33	8.71/8.64	3	<20%
	277	190	-- /6.54		NT
35	278	30	8.49/8.51	3	50%
	279	270	8.06/8.25		NT
	280	480	6.41/6.35	NT	NT

NT = NOT TESTED

NC = Non-Competitive antagonist

5 *Antagonist Activity not observed up to 10 μ M of test compound.

1 Assay A: Angiotensin II Binding Activity

2 Assay B: In Vitro Vascular Smooth Muscle Response

3 Assay C: In Vivo Pressor Response

10

Test Compounds administered intragastrically, except for compounds of examples #1-#2, #4-#25, #27-#29, #30-#79, #108-#109, #111, #118 and #139-#149 which were given intraduodenally.

15

Administration of the angiotensin II receptor antagonist and the aldosterone receptor antagonist may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropyl-methyl cellulose, together with one or more of a lubricant, preservative, surface-active or dispersing agent.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of each active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.01 to 30 mg/kg body weight, particularly from about 1 to 15 mg/kg body weight, may be appropriate.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose of each active component is from about 0.01 to 15 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred

daily dose would be from about 1 to 10 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 15 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 15 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 10 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

In combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 5 mg to about 400 mg, and the AII antagonist may be present in an amount in a range from about 1 mg to about 800 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 400:1 to about 1:160.

In a preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 10 mg to about 200 mg, and the AII antagonist may be present in an amount in a range from about 5 mg to about 600 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 40:1 to about 1:60.

In a more preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 20 mg to about 100 mg, and the AII antagonist may be present in an amount in a range from about 10 mg to about 400 mg, which represents aldosterone

antagonist-to-AII antagonist ratios ranging from about 10:1 to about 1:20.

The dosage regimen for treating a disease condition with the combination therapy of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the active components of this combination therapy invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the components may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The components may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What Is Claimed Is:

1. A method to treat a subject susceptible to or afflicted with cardiofibrosis or cardiac hypertrophy,
5 which method comprises administering a combination of drug agents comprising a therapeutically-effective amount of an angiotensin II receptor antagonist and a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist.
10
2. The method of Claim 1 wherein said epoxy-steroidal aldosterone receptor antagonist is selected from epoxy-containing compounds.
- 15 3. The method of Claim 2 wherein said epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroidal nucleus of a 20-spiroxane compound.
- 20 4. The method of Claim 3 wherein said 20-spiroxane compound is characterized by the presence of a 9 α -,11 α -substituted epoxy moiety.
- 25 5. The method of Claim 2 wherein said epoxy-containing compound is selected from the group consisting of

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ -lactone, methyl ester, (7 α ,11 α ,17 α)-;

30 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 α ,11 α ,17 α)-;

3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -
35 lactone, (6 β ,7 β ,11 β ,17 β)-;

pregn-4-ene-7,21-dicarboxylic acid,9,11-

- epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester,
monopotassium salt, (7 α ,11 α ,17 α)-;
- 5 pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-
17-hydroxy-3-oxo-,7-methyl ester, monopotassium
salt, (7 α ,11 α ,17 α)-;
- 10 3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-
carboxylic acid, 9,11-epoxy-6,7-dihydro-17-
hydroxy-3-oxo-, γ -lactone (6 α ,7 α ,11 α)-;
- 15 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,
methyl ester, (6 α ,7 α ,11 α ,17 α)-;
- 20 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,
monopotassium salt, (6 α ,7 α ,11 α ,17 α)-;
- 25 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
17-hydroxy-3-oxo-, γ -lactone, ethyl ester,
(7 α ,11 α ,17 α)-; and
- 30 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
17-hydroxy-3-oxo-, γ -lactone, 1-methylethyl
ester, (7 α ,11 α ,17 α)-.

6. The method of Claim 1 wherein said
angiotensin II receptor antagonist is selected from
compounds consisting of a first portion and a second
35 portion, wherein said first portion is selected from a
fragment of Formula I:

196

Ar-Alk-L

Ar-L-Ar-Alk-L

Het-L-Ar-Alk-L

Het-L-Het-Alk-L

(I)

5

Ar-L-Het-Alk-L

Het-L-Alk-L

wherein Ar is a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being fully unsaturated or partially or fully saturated;

10

wherein Het is a monocyclic or bicyclic fused ring system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from one or more hetero atoms selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members;

15

20

wherein Alk is an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms;

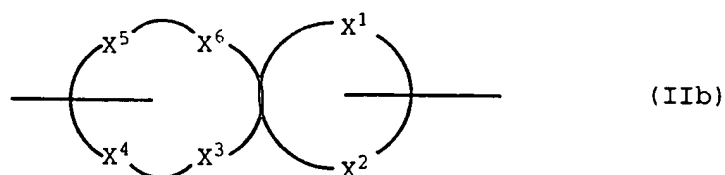
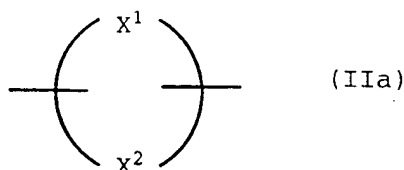
25

wherein L is a straight bond or a bivalent linker moiety selected from carbon, oxygen and sulfur;

30

and wherein said second portion is a monocyclic heterocyclic moiety selected from moieties of Formula IIa or is a bicyclic heterocyclic moiety selected from moieties of Formula IIb:

197



wherein each of X¹ through X⁶ is selected from -CH=, -CH₂-, -N=, -NH-, O, and S, with the proviso that at least one of X¹ through X⁶ in each of Formula IIa and Formula IIb must be a hetero atom, and wherein said heterocyclic moiety of Formula IIa or IIb may be attached through a bond from any ring member of the Formula IIa or IIb heterocyclic moiety having a substitutable or a bond-forming position.

7. The method of Claim 6 wherein said monocyclic heterocyclic moiety of Formula IIa is selected from thienyl, furyl, pyranlyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranlyl, 1,4-pyranlyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl, 1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

8. The method of Claim 7 wherein said bicyclic heterocyclic moiety of Formula IIb is selected from benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxaliny, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiololo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

9. The method of Claim 8 wherein said angiotensin II receptor antagonist compound having said first-and-second-portion moieties of Formula I and II is further characterized by having an acidic moiety attached to either of said first-and-second-portion moieties.

10. The method of Claim 9 wherein said acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

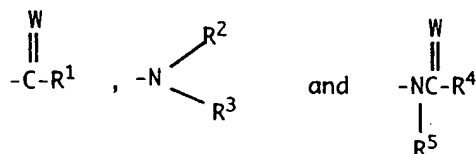


wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties;

wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

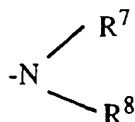
11. The method of Claim 10 wherein said acidic moiety is selected from carboxyl moiety and tetrazolyl moiety.

12. The method of Claim 10 wherein any of the moieties of Formula I and Formula II may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl, aralkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

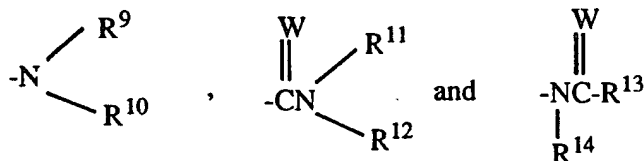


wherein W is oxygen atom or sulfur atom; wherein each of R¹ through R⁵ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR⁶ and

200



wherein Y is selected from oxygen atom and sulfur atom and R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is further independently selected from amino and amido radicals of the formula



15

wherein W is oxygen atom or sulfur atom; wherein each of R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R² and R³ taken together and each of R⁴ and R⁵ taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of R² and R³ taken together and each of R⁷ and R⁸ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido

30

radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

5

13. The method of Claim 12 wherein said angiotensin II receptor antagonist is 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor antagonist is

10 9 α -, 11 α -epoxy-7 α -methoxycarbonyl-20-spirox-4-ene-3,21-dione or a pharmaceutically-acceptable salt thereof.

15

14. The method of Claim 13 further characterized by said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about twenty-to-one of said

20 angiotensin II receptor antagonist to said aldosterone receptor antagonist.

15. The method of Claim 14 wherein said weight ratio range is from about five-to-one to about fifteen-to-one.

25

16. The method of Claim 15 wherein said weight ratio range is about ten-to-one.

30

17. The method of Claim 1 wherein said angiotensin II receptor antagonist is selected from the group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22,

35

WAY-126227, WK-1492.2K, YM-31472, losartan potassium,
E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,
5 L-162441, L-163007, PD-123177, A-81988, BMS-180560,
CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167,
EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739,
HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline,
KRI-1177, L-158809, L-158978, L-159874, LR B087,
10 LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970,
RWJ-46458, S-8307, S-8308, saprisartan, saralasin,
Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731,
BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017,
LY-301875, XH-148, XR-510, zolasartan and PD-123319.

15

18. The method of Claim 17 wherein said
angiotensin II receptor antagonist is selected from the
group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170,
20 EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,
BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,
EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,
LY-235656, PD-150304, U-96849, U-97018, UP-275-22,
WAY-126227, WK-1492.2K, YM-31472, losartan potassium,
25 E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,
L-162441, L-163007 and PD-123177.

30

19. The method of Claim 1 comprising
administering said combination to treat or prevent the
progression of cardiofibrosis.

35

20. The method of Claim 1 comprising
administering said combination to treat or prevent the
progression of cardiac hypertrophy.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/585, 45/06, 31/41 // (A61K 45/06, 31:585), (A61K 45/06, 31:41)	A3	(11) International Publication Number: WO 96/40255 (43) International Publication Date: 19 December 1996 (19.12.96)
(21) International Application Number: PCT/US96/08709 (22) International Filing Date: 5 June 1996 (05.06.96) (30) Priority Data: 08/486,085 7 June 1995 (07.06.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/486,085 (CON) Filed on 7 June 1995 (07.06.95) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): EGAN, James, J. [US/US]; 555 Cherry Street, Winnetka, IL 60093 (US). MCMAHON, Ellen, G. [US/US]; 7925 Camelot, St. Louis, MO 63123 (US). OLINS, Gillian, M. [US/US]; 17507 Summit View, Glencoe, MO 63038 (US). SCHUH, Joseph, R. [US/US]; 2055 Rurline Drive, St. Louis, MO 63146 (US).	(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 23 January 1997 (23.01.97)	
(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST (57) Abstract A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9 α ,11 α -substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 96/08709

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/585 A61K45/06 A61K31/41 //(A61K45/06,31:585),
(A61K45/06,31:41)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 09778 (MERCK & CO LTD) 11 May 1994	1-20
	see page 1-2; figures I-XI	
A	see page 6, line 9; claims 1-3,5-8,10	14-16

Y	WO,A,91 15206 (DU PONT DE NEMOURS; MERCK & CO) 17 October 1991	1-20
A	see page 21, line 12-20; claims 1-4,6-8	14
	see page 24, line 7-12	
	see page 24, line 19-30	
	see page 26, line 1-6	

Y	EP,A,0 481 448 (SQUIBB & SONS INC.) 22 April 1992	1-20
A	see page 11, line 20-45; claims 1,6-8,12,13; examples 12-21	13,17,18

	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

21 November 1996

Date of mailing of the international search report

06.12.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Kanbier, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/08709

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,91 12001 (MERCK & CO INC) 22 August 1991	1-20
A	see page 167	13,17,18
Y	--- THE JOURNAL OF STEROID BIOCHEMISTRY, vol. 32, no. 1b, 1989, pages 223-227, XP000607722 DE GASPARO ET AL: "ANTIALDOSTERONES: INCIDENCE AND PREVENTION OF SEXUAL SIDE EFFECTS" see page 223, right-hand column see page 225	1-20
A	see page 226, right-hand column	13
P,Y	--- WO,A,95 15166 (CURATORS OF THE UNIVERSITY OF MISSOURI) 8 June 1995	1-20
P,A	see page 8-12; claims 1,3 see page 14	13-16
A	--- THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 240, no. 2, 1987, pages 650-656, XP000607709 DE GASPARO ET AL: "THREE NEW EPOXY-SPIROLACTONE DERIVATIVES: CHARACTERIZATION IN VIVO AND IN VITRO" see page 650 see page 653, left-hand column see page 654	1-5,19, 20
A	--- EP,A,0 122 232 (CIBA-GEIGY AG) 17 October 1984 see page 3, paragraph 5 - page 5, paragraph 4; claims 1-8,10 see page 21, paragraph 2 - page 22, paragraph 1; example 17 -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/08709

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-20
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:

Please see next page
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 08709

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the large number of compounds, which are defined by the general formula/description, used in claims 2, 6-12, 17, 18, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, part B, chapter III, paragraph 3.6).

A compound cannot be sufficiently characterized by its pharmacological profile or its mechanism of action as it is done in claim 1 as: "angiotensin II receptor antagonist" and a "aldosterone receptor antagonist". The search has been executed based on compounds specifically mentioned in claims 3-5, 13 and in the examples

Claims searched incompletely: 1, 2, 6-12, 17, 18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/08709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9409778	11-05-94	AU-A- 5449194	24-05-94
WO-A-9115206	17-10-91	NONE	
EP-A-481448	22-04-92	CA-A- 2053148	17-04-92
		JP-A- 4330065	18-11-92
		US-A- 5470975	28-11-95
WO-A-9112001	22-08-91	CA-A- 2075627	14-08-91
		CA-A- 2075637	14-08-91
		EP-A- 0515535	02-12-92
		EP-A- 0517812	16-12-92
		JP-T- 5503530	10-06-93
		JP-T- 5504969	29-07-93
		US-A- 5449682	12-09-95
		WO-A- 9111999	22-08-91
		US-A- 5264439	23-11-93
WO-A-9515166	08-06-95	US-A- 5529992	25-06-96
		AU-A- 1210695	19-06-95
		CA-A- 2177848	08-06-95
		EP-A- 0730458	11-09-96
EP-A-122232	17-10-84	AU-B- 565017	03-09-87
		AU-A- 2685384	18-10-84
		CA-A- 1220781	21-04-87
		DE-A- 3475622	19-01-89
		JP-C- 1586804	19-11-90
		JP-B- 2012479	20-03-90
		JP-A- 59231100	25-12-84
		US-A- 4559332	17-12-85

